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CONTENTS

4 CONFERENCES, COURSES AND SYMPOSIA

9 EDITORIAL
   Imperfect regulation of implants
   Shipley JA

13 MESSAGE FROM THE PRESIDENT
   Big data and medicine
   Rajah L

15 PAEDIATRIC ORTHOPAEDICS
   Body mass index and Blount’s disease:
   a single academic hospital experience
   Kgoedi MN, Rischbieter P, Goller R

21 TUMOURS AND INFECTIONS
   Reactivation of chronic haematogenous osteomyelitis in
   HIV-infected patients
   Siyo Z, Marais LC

26 Minimally invasive CT-guided excision of osteoid osteoma and
   other small benign bone tumours: a single centre case series in
   South Africa
   Sluis Cremer T, Hosking K, Held M, Hilton TL

33 SPINE
   Burden and profile of spinal pathology at a major tertiary
   hospital in the Western Cape, South Africa
   Miseer S, Mann T, Davis JH

40 HIP
   Incidence and risk factors for extended post-operative
   length of stay following primary hip arthroplasty in a
   South African setting
   Dlamini NF, Ryan PV, Moodley Y

47 GENERAL
   Pharmaceutical management of bone catabolism:
   the bisphosphonates
   Raubenheimer EJ, Noffke CEE, Lemmer LB, Slavik T,
   van Heerden WFP, Miniggio HD

54 CPD QUESTIONNAIRE

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LOCAL

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3. SA Shoulder and Elbow Surgeons (SASES)
4. SA Foot Surgeons’ Association (SAFSA)
5. SA Orthopaedic Trauma Society (SAOTS)
6. SA Paediatric Orthopaedic Society (SAPOS)
7. SA Society for Hip Arthroscopy (SASHA)
8. Launch and inaugural meeting of the SA Orthopaedic Oncology and Limb Preservation Society (SOLS)
Contact: Chairman of the SAOA Congress Committee:
Dr Ian Stead, email: iwstead@gmail.com

INTERNATIONAL

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ICJR 7th Annual Revision Hip & Knee Course – Rochester 2019
04 April 2019 – 06 April 2019
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12 April 2019 – 13 April 2019
Utrecht, Netherlands

2nd International Conference on Orthopedics, Rheumatology and Osteoporosis
15 April 2019 – 16 April 2019
Milan, Italy

Atlanta Trauma Symposium 2019
18 April 2019 – 20 April 2019
Atlanta, United States

MAY 2019

EUROSPINE Spring Specialty Meeting 2019
02 May 2019 – 03 May 2019
Frankfurt am Main, Germany

32nd Annual Meeting of the European Musculo Skeletal Oncology Society – EMSOS Florence 2019
15 May 2019 – 17 May 2019
Florence, Italy

22 May 2019 – 24 May 2019
Rome, Italy

IACES 2019 – Madrid International Advanced Course on Elbow Surgery
23 May 2019 – 25 May 2019
Madrid, Spain

JUNE 2019

8th International Congress of Arthroplasty Registries ISAR 2019
01 June 2019 – 03 June 2019
Leiden, Netherlands

ISAR 2019
01 June 2019 – 03 June 2019
Leiden, Netherlands

29th Conference of the European Wound Management Association – EWMA 2019
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South African nurse, Annke Yssel has worked with MSF teams in reconstructive surgical care, in Gaza.

Most of the patients have gunshot wounds

“Most of the patients we see have gunshot wounds in the legs. I soon realized that I was not skilled in treating the patients with ‘ex-fix’ (external fixators) in their legs. I humbly asked the team to teach me how to do this specific wound care procedure. I became the student and my colleagues Subbah and Asad became my teachers.

The faces of the regular patients are becoming familiar to me. Most days I am the only international team member around and they have started to ask me questions. The patients want to know where I am from and why I came to Gaza. It is very nice to be able to introduce myself in Arabic and explain that I am a nurse from South Africa.

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Imperfect regulation of implants

Prof JA Shipley

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Towards the end of last year, a prominent UK newspaper carried a leading article ‘Revealed: faulty medical implants harm patients around the world’. This was followed shortly after by a BBC News article on the same subject. The Implant Files Project, an international group coordinated by the International Consortium of Investigative Journalists, published some impressive statistics about implant problems. The main targets were meshes for pelvic floor and hernia reconstruction, breast implants, cardiac pacemakers and a contraceptive, but orthopaedics did not escape unscathed. Problems with total hip, knee and intervertebral disc replacements also featured prominently. Even allowing for journalistic dramatisation and over-simplification, the figures quoted are worrying. Between 2015 and 2018, 62 000 adverse events with implants were reported in the UK alone, a third of them causing serious complications, including 1 004 deaths. In the USA the FDA recorded 5.4 million events over the past decade, with 500 000 implants requiring removal, and 83 000 deaths.

Prof Derek Alderson, the president of the Royal College of Surgeons, was quoted as saying there had been enough incidents involving flawed devices to ‘underline the need for drastic regulatory changes’, including the introduction of mandatory national registries for all implantable devices.

‘In contrast to drugs, many surgical innovations are introduced without clinical trial data or centrally held evidence,’ he said. ‘This is a risk to patient safety and public confidence.’

Three years ago, I wrote in an editorial for this journal, ‘New techniques need to be validated independently before, not after, they are released on the market. And as commercially naive, enthusiastic and adventurous surgeons we must learn not to confuse novelty with progress’. I still feel the same, and think we need improved enforcement of the present imperfect regulation of implants.

The criticisms of the present system can be reduced to the following:

• absence of independent clinical trials of implants in humans (as opposed to pigs!) before their release on the market
• failure of manufacturers to respond constructively to complaints about their products
• failure of manufacturers to reveal previous rejections by regulatory bodies when making application to a new body
• considerations of commercial confidentiality obstructing enquiries
• acceptance by a regulatory body of an implant on the grounds of approval by another regulator, or similarity to another implant, without performing an independent evaluation

Medical implants in the USA are licensed by a single body, the reputable FDA, although the process is slow. But in the EU there is no overall regulator; and a ‘CE mark’ of approval can be issued by any one of 58 ‘Notified bodies’. These are non-governmental companies, and if one declines approval of a product, application may be made at another one with no need to disclose the rejection elsewhere. Regulation in the EU is due to be upgraded in 2020, but apparently there is doubt as to how effective this will be. The Medicines Control Council of South Africa is the official regulator in this country but it is dysfunctional.

So should we simply rely on European or USA licencing for protection even though their processes are open to criticism? I think this would be a mistake for two main reasons and believe that we need to evaluate any implant under South African conditions, while remaining alert for problems encountered in other countries. My first reason is that different countries have different profiles of patients and implant use, and different surgical traditions or preferences, often regional. This may skew results in different locations, such as our country, and local registers are needed to identify poor performers. There is a second important aspect. Implant problems can be divided into design errors, which would apply to every implant used, and manufacturing problems where a certain batch of implants may be flawed for some reason. Design errors in devices from reputable manufacturers will become obvious in time, especially in countries where large numbers of the implant are used and registers are kept. This would allow recognition of a problem implant irrespective of where it is used. Manufacturing problems and implants from little known manufacturers may be different, however. In a small market like South Africa, it would be quite possible for an occasional sub-standard batch of implants from a recognised company to form a substantial proportion of an importer’s order. This would cause a localised problem with an implant that is not noticeable against the background of its success elsewhere, and would only be picked up by a register in the area where they are concentrated. Another problem is the use of cheap implants from unknown sources often in the Far East. They usually have no history of performance and are imported by opportunistic entrepreneurs, often to supply a Provincial tender. Again, any low-cost devices that are below standard would only be recognised if their use is recorded and tracked. So South African implant registers may be very important for the identification of such problem batches or imports, and the patients who are at risk following their use.

I agree with Prof Alderson that mandatory registers for all implants have become necessary. South African implant registers...
would certainly make a contribution to the global experience, but they are probably more valuable for their ability to recognise inappropriate implant use and manufacturing defects in this region. The government cannot be expected to organise this without our help, and it would be ridiculous to expect the fiercely competitive orthopaedic industry to police itself. I believe the onus is on each surgeon to record his implant use in a register owned and administered by the respective professional body – in our case the SAOA and its sub-groups. We are all aware of past problems in South Africa with arthroplasty registers, and this would probably need some form of legislation to motivate our less compliant colleagues. As a back-up, the hospital groups should also be made responsible for recording implant use, including details of the patient and surgeon. Costs could be recovered from a small levy added to the price of each implant. The medical aids could be expected to support such registers as they would benefit financially from identifying and eliminating substandard hardware and their attendant complications. Medical aid and hospital administration systems could certainly be programmed to record and forward data to central registers at minimal cost and inconvenience to all concerned.

I have written this editorial as one with no experience of implant registers or the practical problems around them. I realise this is a controversial subject but I hope that a dispassionate, objective examination of the matter will result in increased understanding and support for the SAOA and the leaders in our speciality in their efforts to achieve this ideal. I believe we have a professional obligation to do so.

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Big data and medicine

Leon Rajah

MESSAGE FROM THE PRESIDENT

South African Orthopaedic Journal
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‘We are on the verge of a digital revolution across every aspect of this sector, from the lab bench to the patient’s bed side’.1,2

It is predicted that three emerging technologies will drive the next wave of medical innovation:

1. Internet of things: For example, wearable devices can track measures such as walking speed, balance and movement. Such real-time data provides a better understanding of disease progression and impact of treatment.

2. Artificial intelligence (AI) and machine learning: These technologies will revolutionise the way we interrogate data.

3. Emerging data platforms: These will allow unprecedented computing power and advances in data management systems for analysis and insight generation referred to as big data.

Big data refers to the analysis of massive amounts of data points to gain novel insight; and its key characteristics may be understood by considering data, method and purpose.3

Data

Big data is a massive shift in the ability to collect and analyse data quickly and cheaply. In the future we will routinely collect and analyse massive data sets from a larger number of individuals relevant to a phenomenon; and when possible, analyse all data collected, rather than just data samples.

With big data, volume may be traded off against quality. The ‘unreasonable effectiveness of data’ maintains that heterogeneous sources for data of limited quality may be better if one generates a huge amount of it, compared to only a small amount of data at high quality.4 Using comprehensive data leads us to ask a further question: when do we stop collecting data and what do we do with ‘new’ data? Big data suggests tentativeness; learning is a summary of what is known of a dynamic phenomenon and necessitates re-evaluation at regular intervals.

Method

A big data approach requires the use of AI and its application to machine learning.4,5 AI refers to the ability of a machine to perform cognitive functions usually associated with the human mind (perception, reasoning, learning and problem solving). Machine learning is the application of AI to massive data sets using complex self-learning algorithms to detect patterns, make predictions and generate hypotheses. The potential of AI is enormous: In 2017, Google’s Alpha Zero Program Self-Learning AI chess programme taught itself chess with no human instruction, and after only 8 hours beat the then reigning 2016 World Computer Chess Champion Stockfish 8.

Purpose

There are two distinctive features of big data analysis. The first is the inductive nature of big data systems – analysis of a massive number of data points to identify patterns that prompt hypothesis generation; this in contrast to the conventional research method of using data to validate a human hypothesis. The second is that big data approaches are correlational. Big data does not demonstrate causality, is agnostic to cause and has been criticised for lacking causal explanatory value.

This is not a new argument: in 1847 the hygienist Semmelweis identified that hand washing with chlorine in maternity wards dramatically decreased mortality rates.5 Most of his colleagues rejected the findings (he inferred an incorrect underlying cause) and resisted hand washing with chlorine, causing the unnecessary deaths of tens of thousands. Big data insights are going to raise similar issues in the future: What is sufficient evidence to act? How high is the burden of proof?

The approaches need not be exclusionary. In a recent study of Alzheimer’s disease, millions of variables were measured following DNA and RNA sequencing in different brain regions. Conclusions were reached by allowing the data to speak to a likely driver of disease. The data analysis identified the immune system and microglial cells as a key driver of disease (as opposed to traditional concepts relating to tangles or plaques).6 This raised possible novel therapies, which may be evaluated using hypothesis-testing in prospective randomised controlled trials. Big data may herald a change to a more staged discovery process – with correlational results and ensuing causal inquest.

The usefulness of the big data approach in health care remains disputed, however – does it provide a future with novel insights or does it create more noise that drowns out true signals? Jacofsky refers to these as: a lack of data set reliability and clarity; a preponderance of unstructured data; ineffective and inaccurate measures transposed to manage the behaviour of providers and income from payer claims or coders; a lack of intersystem reliability and inconsistent value of output from a system (analogous to a calculator providing a different answer to the same calculation).7 Big data can impose the same challenges as small data; and adding more data without physicians to control and standardise definitions will most often not solve but merely magnify the problem.

Conclusion

Big data enthusiasts propose that medicine has changed to an information science.8 Popular literature declares the physical
examination of a patient redundant. In our prime directive – ‘the only interest to be served is the interest of the patient’ – is embedded that human spirit to defend the integrity of clinical practice, thought and innovation; and posit clinical medicine as integral to a defence against a future dominated by digital dictatorship, financial oligarchy and human redundancy.

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Body mass index and Blount’s disease: a single academic hospital experience

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Abstract

Background: Blount’s disease is a developmental disorder of the proximal tibia with progressive varus, flexion and internal rotation deformity. It is often seen in overweight children and strongly associated with obesity. As the prevalence of childhood obesity is increasing worldwide, the incidence of Blount’s disease has been noted to be on the increase as well. In the South African population, most children are malnourished with high levels of undernutrition compared to other middle-income countries. We hypothesised that in our institution, patients with Blount’s disease have a body mass index (BMI) lower than reported in studies from mainly developed countries. The aim of the study was to investigate the relationship between BMI and Blount’s disease in a South African academic institution.

Methods: All clinical and radiological records of patients with Blount’s disease at a tertiary hospital in South Africa over a six-year period were retrospectively reviewed. Five patients did not meet inclusion criteria and were excluded from the study. Data collected included patients’ demographics, weight, height and radiological investigations. A control group of randomly selected paediatric orthopaedic patients was studied.

Results: A total of 39 Blount’s patients (19 females, 20 male) were studied. All the Blount’s patients were of black ethnicity. There were nine patients with early-onset and 30 patients with late-onset Blount’s disease. The mean BMIs for Blount’s disease and control groups were 26 kg/m² and 20 kg/m² respectively (p<0.001). There was no statistical difference in sex, laterality, BMI and BMI-percentiles (BMI%) between early-onset and late-onset Blount’s disease. There was no relationship between BMI and severity of Blount’s disease deformities.

Conclusion: High BMI is associated with Blount’s disease in the cohort studied. There was no relationship between increasing BMI and severity of Blount’s deformities. No relationship was found between sex, onset or laterality and Blount’s disease in our study.

Level of evidence: Level 4

Key words: Blount’s disease, body mass index, childhood obesity, metaphyseal–diaphyseal angle, tibio-femoral shaft angle
Introduction

Blount’s disease is a developmental condition characterised by disordered endochondral ossification of the medial part of the proximal tibial growth plate resulting in multi-planar deformities of the lower limb.1,2 Secondary to the asymmetrical growth with relative inhibition of the postero-medial portion of the proximal tibial growth plate, a three-dimensional deformity of the tibia develops with varus, procurvatum (apex anterior), and internal rotation along with possible limb shortening in unilateral cases.1,2 This entity can lead to a progressive deformity with gait abnormalities, limb-length discrepancy, and premature arthritis of the knee.1,2 Blount’s disease is classified into early-onset (infantile) and late-onset based on whether the limb deformity develops before or after the age of four years.2,4 It is classified radiologically by Langenskiold into six progressive stages per severity of the deformity to help in prognosticating patients’ outcome.4-7 The incidence of Blount’s disease in South Africa was estimated to be 0.03% three decades ago.8

The aetiology of Blount’s disease remains unknown, though multifactorial origin is proposed with genetic and mechanical components contributing to its development.3 There is a predisposition of black children to develop Blount’s disease compared to other racial groups.3 Blount’s disease has been linked to increasing weight and vitamin D deficiency.1,2,9,10 A number of studies show a strong correlation between Blount’s disease and obesity.3,10-14 Lisenda et al. found no independent association between vitamin D deficiency and Blount’s disease in their study in South African children.15 Obesity has been shown to greatly increase the medial compartment pressure and contribute to the development of Blount’s disease by the Heuter-Volkmann principle.16

Limited research is inconclusive on the relationship between increasing body mass index (BMI) and the severity of Blount’s disease deformity.1,11,13 A strong correlation has been found only between morbidity and radiological deformities of early-onset Blount’s disease.13 As the prevalence of childhood obesity is increasing worldwide, Blount’s disease has been noted to be on the increase as well.1,16 In a retrospective study of 44 Blount’s disease patients by Sabharwal et al., the average BMI was 35.6, with the average BMI of 29.2 for early-onset and 39.7 for late-onset Blount’s disease.13

Childhood obesity has doubled in the past three decades. The percentage of children aged 6–11 years who were obese increased from 7% in 1980 to nearly 16% in 2012 in the United States.17 Similarly, the percentage of adolescents aged 12–19 years who were obese increased from 5% to nearly 21% over the same period.17 In 2012, more than one-third of children and adolescents were either overweight or obese.17 It has been estimated that over 22 million children under the age of 5 years are obese worldwide.18 The prevalence of being overweight in Africa and Asia averages below 10% while in America and Europe it averages above 20%.18 In the South African population, many children are malnourished compared to other middle-income countries.19-23 Micronutrient malnutrition is regarded as a public health problem of considerable significance in South Africa.19,22-23 South African children aged 1 to 9 years have an intake of less than 67% of the recommended dietary allowances (RDAs) for energy, calcium, vitamin D and other micronutrients.19,22,23 In a national study conducted in 2004, 10% of children were classified as overweight and 4% as obese in South Africa.22 The Health of the Nation Study, estimated an increase in overweight from 1.2% to 13% and in obesity from 0.2% to 3.3% over the period from 1994 to 2004, and more recent studies showed a mean prevalence of just over 15% for overweight and obesity combined.24

The purpose of this study was to investigate the BMI profile and demographics of patients with Blount’s disease in the South African context and determine the relationship between body weight and Blount’s disease and the severity of angular deformities. We hypothesised that in our institution, patients with Blount’s disease have a higher BMI than the general paediatric population, but still lower than reported studies from mainly developed countries. The second hypothesis was that increasing BMI is associated with worsening angular deformities.

Material and methods

A retrospective review of clinical and radiological records was conducted of all patients with Blount’s disease that attended the Paediatric Orthopaedic Unit from 1 January 2011 to 31 December 2016. Patients’ details were obtained from the surgical database and outpatient records. Patients’ folders were retrieved from the records department. Radiological images of all patients were available from the hospital’s picture archiving and communication system (PACS). All patients diagnosed with Blount’s disease were included in the study. Patients were grouped into four ethnicities, i.e. black, white, coloured and Indian. Incomplete clinical records, other congenital abnormalities and patients over 20 years of age were excluded from the study.

A randomised control group of 100 paediatric orthopaedic patients was included in the study to achieve a ratio of at least 2:1 for statistical analysis. This included patients that were treated for injuries with clinical records of weight and height. Patients with other congenital abnormalities/deformities and patients over 20 years of age were excluded from the control group. A simple randomisation method was utilised to obtain a representative sample of the control group from 1 January 2016 to 31 December 2016. The control group consisted of patients seen in 2016, grouped by sex. Each was allocated a number and a random number generator was utilised to obtain a sample of 50 patients for each sex. BMIs were calculated from the patients’ weight and height records. The BMIs were interpreted as follows: <18.5 kg/m² as underweight, 18.6–24.9 kg/m² as normal, 25–30 kg/m² as overweight and >30 kg/m² as obese.2 BMIs were plotted using the 2000 Centre for Disease Control and Prevention age- and sex-specific charts for every patient.

Patients’ radiological images were studied for classification of Blount’s disease using the Langenskiold classification system. This is a staging system of Blount’s disease according to the degree of metaphyseal–epiphyseal changes seen on radiographs used to prognosticate outcomes.3,4,5 Stage I is defined as presence of medial epiphyseal beaking; stage II is described as a saucer-shaped defect of medial metaphysis; stage III is when the saucer defect deepens into a step; stage IV is when the epiphysis is bent down over the medial beak; stage V when there is the presence of a double epiphysis; and stage VI when there is development of a medial physeal bony bar.4,5 These were further categorised as low grade (Langenskiold stages I–IV) and high grade (Langenskiold stages V–VI) Blount’s disease.7,25 Tibio-femoral angles (TFA) were calculated on the PACS images and recorded for each patient. X-rays were full weightbearing with the patella facing forward. All data collected was recorded onto Microsoft Excel spreadsheet for analysis. Ethics approval was obtained prior to commencement of the study.

Statistical methods

The descriptive statistics were used with the assistance of a statistician. Standard deviation and ranges, with 95% confidence intervals for body mass indices in children with Blount’s disease and
the control group were calculated. The t-test and Wilcoxon rank-sum (Mann-Whitney) test were used to determine differences in BMI between early-onset and late-onset Blount's disease children.

Cross-tabulations of categorical variables with Fisher's exact and chi-squared tests were done to assess for associations. The frequency distributions in terms of BMI and BMI% of early-onset and late-onset Blount's disease were compared using the chi-squared test. The two-sample Wilcoxon rank-sum (Mann-Whitney) test was used to determine statistically significant differences in BMI between the Blount's disease group and the control group, controlling for age. Pearson's correlations were used to assess the relationship between BMI and angular deformity (TFA), and a univariate logistic regression model using BMI to predict the Langenskiold classification for severity was assessed. Significance was determined at p-value <0.05 for all statistical analyses. Statistical analysis was done using STATA 14 (StataCorp, 4905 Lakeway Drive, College Station, Texas, USA).

### Results

Forty-four Blount's disease patients were identified. Five patients were excluded from the study (three had no weight and height records and two had no radiographs on PACS). Records and radiographs of 39 patients were retrospectively analysed. There were 20 male patients and 19 female patients with a mean age of 7.5 years (range: 1–15). A summary of the patient data is given in Table I. There was no difference in sex distribution of both early-onset (infantile) and late-onset (juvenile and adolescent) Blount’s disease patients. The mean age was 3 years (range: 2–4) for early-onset Blount’s disease and 10 years (range: 5–17) for late-onset Blount’s disease patients. All Blount’s disease patients were of black ethnicity. A total of 100 control patients were studied. The control group had 50 male and 50 female patients with a mean age of 8.4 years (range: 2–17).

The mean BMI for Blount’s disease patients was 26.5 kg/m² (range: 12–44) with early-onset Blount’s patients having a mean of 24.2 kg/m² (range: 12–44) and 27.7 kg/m² (range: 12–43) for late-onset Blount’s patients (Table II). There was no statistical difference between the mean BMI of early-onset and late-onset Blount’s disease patients (p=0.3944), although the late-onset group had a slightly higher mean BMI. The mean BMIs of male and female patients with Blount’s disease were 27.7 kg/m² and 25.3 kg/m² respectively (p=0.4489).

There was no association between laterality and onset of Blount’s disease (early vs late) with Pearson chi-squared = 0.22 with p-value = 0.64 and Fisher’s exact = 0.72. There was a statistically significant difference between the mean BMI of patients with unilateral disease 23.2 kg/m² (range: 12–40) and bilateral disease 29.9 kg/m² (range: 13–44) with p-value = 0.0275). The mean BMI for the control group was 20.2 kg/m² (range: 12–36). There was a statistically significant difference between the mean BMI of Blount’s disease patients and the control group (p-value = 0.0005).

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Table III presents a comparison of BMI% between Blount’s disease patients and the control group based on the CDC 2000 percentile chart.

### Table I: Summary of Blount’s patients’ demographic data

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Late</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>9</td>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>4</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Bilateral</td>
<td>5</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Langenskiold classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Stage II</td>
<td>9</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Stage III</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Stage IV</td>
<td>0</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Stage V</td>
<td>1</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Stage VI</td>
<td>0</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

### Table II: Mean BMI values of the subgroups of Blount’s disease patients

<table>
<thead>
<tr>
<th>Onset</th>
<th>Mean BMI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>24.2</td>
<td>0.459</td>
</tr>
<tr>
<td>Late</td>
<td>27.7</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Mean BMI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>27.7</td>
<td>0.4489</td>
</tr>
<tr>
<td>Female</td>
<td>25.3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laterality</th>
<th>Mean BMI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>23.2</td>
<td>0.0275</td>
</tr>
<tr>
<td>Bilateral</td>
<td>29.9</td>
<td></td>
</tr>
</tbody>
</table>

### Table III: Classification of Blount’s patients and the control group based on BMI percentile ranges (CDC 2000 percentile chart)

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Blount’s</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5th (underweight)</td>
<td>13% (5)</td>
<td>3%</td>
<td>5.76%</td>
</tr>
<tr>
<td>5th to 85th (normal)</td>
<td>15% (6)</td>
<td>46%</td>
<td>37.4%</td>
</tr>
<tr>
<td>85th to 95th (overweight)</td>
<td>13% (5)</td>
<td>11%</td>
<td>11.51%</td>
</tr>
<tr>
<td>&gt;95th (obese)</td>
<td>59% (23)</td>
<td>40%</td>
<td>45.32%</td>
</tr>
</tbody>
</table>

Fisher’s exact = 0.002
Figure 1. Body mass index categories of Blount’s disease patients and the control group

<table>
<thead>
<tr>
<th>BMI category</th>
<th>Percentage of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>31</td>
</tr>
<tr>
<td>Normal</td>
<td>13</td>
</tr>
<tr>
<td>Overweight</td>
<td>23</td>
</tr>
<tr>
<td>Obese</td>
<td>33</td>
</tr>
</tbody>
</table>

- **Blount’s**
- **Control**

Figure 2. Radiograph of a 3-year-old child with bilateral limb involvement, early-onset Blount’s disease

Figure 3. Standing antero-posterior (AP) radiograph of a 9-year-old female patient with Langenskiold stage VI late-onset Blount’s disease of the right limb
A total of 58 knees were studied radiologically (19 bilateral, 20 unilateral disease). Examples of the cases are illustrated in Figures 2 and 3. Using the Pearson correlations, no relationship was found between BMI and TFA (r=0.0342, p=0.8364). Using BMI to predict the Langenskiöld classification for severity by the univariate logistic regression model, no association was found between BMI and Langenskiöld classification (p=0.453). The mean TFA was 26.88° (range: 12–50) for early-onset disease and 27.4° (range: 4–54) for late-onset disease. Using cross-tabulation and Fisher’s exact test to assess for an association between onset and Langenskiöld classification, eight of nine patients with early-onset Blount’s had low-grade (I–IV) Blount’s disease (88.9%) whereas 56.7% of patients with late-onset Blount’s disease had high-grade (V–VI) Blount’s disease. This was statistically significant with p=0.023.

Discussion

The results our cohort show that patients with Blount’s disease have a higher BMI compared to the general paediatric population. These results are comparable to studies reported in developed and other developing countries. However, the mean BMI for Blount’s disease patients was significantly lower than in the existing literature.13

Sex

In our study population, Blount’s disease affected both sexes equally with a comparable number of unilateral and bilateral cases. Similarly, there was an equal presentation of both sexes in early-onset and late-onset Blount’s disease groups. A recent meta-analysis by Rivero et al. found that patients with early-onset Blount’s disease were more likely to be females than males (61% vs 39%; p=0.01).3 Inaba et al. in a multi-centre study in Japan found that there were more females in both early-onset and late-onset Blount’s disease. On the contrary, Montgomery et al. found that Blount’s disease had a statistically significant positive association with patient’s sex, with males 8.16 times more likely to have Blount’s disease compared with females.10 Sabharwal et al. in their study of 51 Blount’s disease patients also found more males affected than females (32 males vs 19 females).21 Our study found that male patients had a higher mean BMI value than their female counterparts. Sabharwal et al. also found a higher BMI in males than females (38.2 vs 32.1 p=0.07) in his study of 45 patients with Blount’s disease.13 On the contrary, Pirpiris et al. found no statistical difference in BMI between males and females, with females having slightly higher BMI values than males (24.6 kg/m² in males vs 26.1 kg/m² in females, p=0.10).11

Laterality

Our study found that patients with bilateral disease had significantly higher BMIs compared to patients with unilateral disease. Sabharwal et al. also found that patients with unilateral Blount’s disease have a lower mean BMI than patients with bilateral Blount’s disease (34.7 kg/m² and 36.8 kg/m² respectively, p=0.53).13 There was no relationship between the onset of Blount’s disease and laterality, with equal numbers of unilateral and bilateral cases found in each group. This contrasts with the meta-analysis by Rivero et al. which found more bilateral cases in early-onset Blount’s disease patients and a high incidence of unilateral cases in late-onset (adolescent) Blount’s disease patients.3 Our limited number of early-onset Blount’s disease rendered comparison inconclusive.

Body mass index

The mean BMI values of our study population are significantly lower than those reported in the literature. A retrospective study of 45 Blount’s disease patients by Sabharwal et al. found a mean BMI of 35.6 kg/m² with mean BMI of 29.2 kg/m² for early-onset Blount’s disease and 39.7 kg/m² for late-onset Blount’s disease.13 In our study, the mean BMI was 26.5 kg/m² with a mean BMI of 24.2 kg/m² for early-onset and 27.2 kg/m² for late-onset Blount’s disease. Malnutrition and environmental effects may have contributed to the difference.15,21-23

Race

Our study population with Blount’s disease consisted only of the black race. Although a conclusion cannot be reached, there seems to be a high predisposition of Blount’s disease in black children. Rivero et al. found a greater prevalence of Blount’s disease among black children, although this predisposition was stronger in late-onset Blount’s disease.3 A recent study by Lisenda et al. from South Africa also found all the patients in their study to be of black race.16 This forms a strong basis to suggest the relationship between black race and Blount’s disease.

Onset

Our study had only nine (23%) early-onset Blount’s patients compared to 30 (77%) late-onset Blount’s disease patients. Although late-onset Blount’s patients had a higher mean BMI compared to early-onset Blount’s disease, this was not found to be statistically significant. These results are similar to a study by Sabharwal et al. which found that early-onset Blount’s disease patients have lower BMI values than late-onset Blount’s disease patients.13

Severity

Our study found no statistical difference in severity of angular deformity using TFA in both the early-onset and late-onset diseases and no association with BMI. Dietz et al. have investigated the relationship between obesity and angular deformities in 15 children diagnosed with Blount’s disease and found a strong relationship between body weight, TFA and varus deformities.12 In a study by Sabharwal et al., a linear correlation was found between obesity and radiographic changes in children with early-onset Blount’s disease (r=0.74, p < 0.0001) and children with BMI values greater than 40 kg/m² who have late-onset Blount’s disease. No relationship was found in late-onset Blount’s disease patients with BMI <40 kg/m².13

Langenskiöld classification

Our study found that patients with early-onset disease had low-grade Blount’s disease (i.e. Langenskiöld I–IV) and more than 50% of patients with late-onset Blount’s disease had high-grade disease (i.e. Langenskiöld V–VI). This finding was expected as Langenskiöld staging is associated with patient age.2,4-5 There was no relationship found between BMI and the Langenskiöld classification system. To our knowledge, no study was done to assess the effect of BMI on the Langenskiöld classification, but several studies were conducted to assess the relationship between BMI and severity of angular deformity using TFA angles.

The study limitations include the retrospective nature of the study and the limited number of patients due to the low incidence of this condition. The study had a small group of patients with early-onset Blount’s disease, thus conclusions between the two groups could
not be reached. Although increased BMI has a strong association with Blount’s disease and probably influences the severity of angular deformities, other factors that may contribute to these changes were not assessed, i.e. vitamin D deficiencies and early walking age although vitamin D deficiency was not found to be associated with Blount’s disease in a recent study.15

Conclusion
Our study demonstrates that our cohort with Blount’s disease has a higher BMI than the control population at our institution. Contrary to existing literature, no relationship was found between sex, onset or laterality and Blount’s disease in our study. There was also no significant difference in BMIs between early-onset and late-onset Blount’s disease patients or the severity of the deformities. Although our study only had black patients, a larger multi-centre study is required in the South African population to assess the relationship between race and Blount’s disease and to assess the genetic aetiology that may be responsible for the black racial predilection. Our findings support the association between BMI and Blount’s disease in children. Measures aimed at decreasing weight and thus childhood obesity may have some effect on the number of children with this condition.

Ethics statement
The study was conducted after written approval from the Academic Hospital management. Approval from the University MMed committee was obtained. The Faculty of Health Science’s Ethics committee approval was obtained (Protocol number: 5/2017) prior to the commencement of the study. All patients' records were assigned a study number and no patient details were divulged in order to protect their confidentiality.

Declaration
The authors declare authorship of this article and that they have followed sound plagiarism policies.

Acknowledgements
We wish to thank the staff at Paediatric Orthopaedic unit, for their continuous dedication and management of these patients with Blount’s disease.

Author contributions
Kgoedi MN – main author, study conceptualisation, protocol preparation, collection and interpretation of data and preparation of the manuscript
Rischbieter P – contributed to study conceptualisation, preparation of the protocol and collection of data
Goller R – study supervisor from study conceptualisation, review of protocol, preparation and revisions of the manuscript

References
Abstract

Background: The aim of the study is to determine the prevalence of HIV infection among adult patients with reactivation of haematogenous chronic osteomyelitis.

Methods: A retrospective analysis of prospectively collected data from 143 adult patients with chronic osteomyelitis.

Results: A total of 143 patients were included in the study group, with a mean age of 38 years (range 14–78 years). Twenty-two per cent (n=31) of patients were diagnosed with reactivation of chronic haematogenous osteomyelitis, while 78% of patients had contiguous chronic osteomyelitis (29% [n=42] post-operative and 49% [n=70] post-traumatic, respectively). Forty (28%) patients were found to be HIV positive with a mean CD4 count of 414 cells/mm³ (range 13–1 034 cells/mm³). Twenty-four (60%) of patients with HIV were on antiretroviral therapy at time of diagnosis. The prevalence of HIV infection among patients with contiguous (post-operative or post-traumatic) infections was 32%, in comparison to 13% in the group with reactivation of chronic haematogenous infections (p=0.04; OR 3.2; 95% CI 1.0–9.8).

Conclusion: The prevalence of HIV infection among patients with reactivation of chronic haematogenous osteomyelitis appeared to be lower than that seen in patients with chronic osteomyelitis from other causes and lower than that seen in the general population in South Africa.

Level of evidence: Level 4

Key words: haematogenous, osteomyelitis, HIV, AIDS
Introduction

The total number of people living with human immunodeficiency virus (HIV) in South Africa is currently estimated at approximately 7.06 million. In the age group 15–49 years, the national prevalence is estimated at 16.8%. The prevalence in KwaZulu-Natal, the second largest province in South Africa with a population of approximately 11.1 million people, is currently estimated at 21.5%. HIV infection results in a combination of immune suppression and chronic inflammation through the mechanisms of immune exhaustion with effecter T-cell dysfunction and immune senescence with premature aging of the immune system. The resulting neutrophil, monocyte and B-lymphocyte abnormalities lead to a decreased capacity for bacterial phagocytosis and an increased rate of bacterial infections. Methicillin-resistant Staphylococcus aureus infection is, for example, 6–18 times more common in HIV patients than in the general population. HIV co-infection is presumed to be among the major contributing factors to the pathogenesis of bone infection.

Chronic osteomyelitis can be defined as a biofilm-based infection where the majority of pathogens are sessile-based and are resiliently attached to the nidus of infection. In the case of chronic haematogenous osteomyelitis, the nidus of infection is typically a sequestrum that is formed following acute osteomyelitis in childhood. The appropriate treatment of acute haematogenous osteomyelitis has resulted in a drastic decrease in the incidence of chronic osteomyelitis of haematogenous origin in the developed world; however, it remains fairly common in the developing world. Owing to the unique characteristics of the causative organisms, reactivation of chronic osteomyelitis may occur as much as 65 years following the initial infection. These characteristics include the internalisation of bacteria by osteoblasts which is mediated by the sigma B regulon in the case of Staphylococcus aureus. The exact cause of the reactivation of infection has, however, not been clearly defined but it is believed to be associated with a decrease in local or systemic immune protection. Jellis reported a possible increase in haematogenous osteomyelitis in patients with HIV infection. This was however only a comment and further data on the topic was not provided. To the best of our knowledge, there is currently no data on the reactivation of chronic haematogenous osteomyelitis in HIV patients. The aim of the study is to determine the prevalence of HIV infection among adult patients with reactivation of haematogenous chronic osteomyelitis.

Materials and methods

A retrospective descriptive study was performed on prospectively collected data from consecutive patients seen at a tertiary-level tumour and sepsis unit with chronic osteomyelitis. All adult patients over the age of 14 years assessed from January 2011 to December 2014 were included in the study. Patients excluded from the study were those with atypical infections including fungal, parasitic and tuberculosis, acute post-operative infection, periartificial joint infection or hand sepsis.

Following ethical approval from the relevant biomedical ethics review board, data were collected with respect to patient age, cause of osteomyelitis (haematogenous or contiguous), physiological stage and anatomical nature of the disease according to the Cierny and Mader classification system, HIV status, CD4 count and the presence of antiretroviral therapy.

For the purposes of this study chronic osteomyelitis was defined as an infection involving bone, with a duration of at least ten days, where the causative organisms were thought to have persisted either intracellularly or in interactive biofilm-based colonies. Haematogenous chronic osteomyelitis was defined as the reactivation of chronic osteomyelitis resulting from a previous episode of acute osteomyelitis of haematogenous origin. Contiguous chronic osteomyelitis was defined as chronic osteomyelitis resulting from a prior open fracture (post-traumatic) or operative intervention (post-operative).

All patients were screened for HIV infection. Following clinical, radiological and biochemical evaluation, patients were classified according to a modified version of the original Cierny and Mader classification system (Table I). In terms of the physiological status of the host, the Cierny and Mader classification system was modified in order to provide a more pragmatic and objective definition of a C host. A patient was classified as a C host if one major or more than two minor risk factors were present (Table II). In order to remove any ambiguity during classification of the anatomical nature of the disease, this was performed prior to, rather than following, the debridement.

Statistical analysis was performed using Stata 13.0 (StataCorp. College Station, Texas). Continuous variables were reported as mean (± SD) or median (with interquartile range) and categorical variables as numbers and percentages, unless otherwise stated. Categorical data were compared using the Fisher’s exact test or the chi-square test. All tests were two-sided, and the level of significance was set at p<0.05.

### Table I: Modified version of the original Cierny and Mader classification system that served to guide treatment strategy selection

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristic</th>
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<tbody>
<tr>
<td><strong>Physiological</strong></td>
<td></td>
</tr>
<tr>
<td>Type A host</td>
<td>No risk factors</td>
</tr>
<tr>
<td>Type B host</td>
<td>Fewer than three minor risk factors</td>
</tr>
<tr>
<td>Type C host</td>
<td>One major and/or three or more minor risk factors</td>
</tr>
<tr>
<td><strong>Pathoanatomy</strong></td>
<td></td>
</tr>
<tr>
<td>I – Medullary</td>
<td>No cortical sequestration</td>
</tr>
<tr>
<td>II – Cortical</td>
<td>Direct contiguous involvement of cortex only</td>
</tr>
<tr>
<td>III – Combined (stable)</td>
<td>Both cortex and medullary regions involved</td>
</tr>
<tr>
<td>IV – Combined (unstable)</td>
<td>As for III plus unstable prior to debridement</td>
</tr>
<tr>
<td><strong>Nidus</strong></td>
<td></td>
</tr>
<tr>
<td>Sequestrum</td>
<td>Cortical sequestrum present</td>
</tr>
<tr>
<td>Implant</td>
<td>Biofilm-based infection in presence of implant</td>
</tr>
<tr>
<td>No identifiable nidus</td>
<td>Minimal necrosis osteomyelitis</td>
</tr>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>Patient able to perform ADL (activities of daily living)</td>
</tr>
<tr>
<td>Severe</td>
<td>Unable to perform ADL</td>
</tr>
</tbody>
</table>
Considerable controversy remains regarding the association of HIV infection and the development of bone infections. In the 1990s, Jellis and Hoekman independently reported an infection rate of operatively treated fractures of 24% and 33% in symptomatic HIV patients.10,12 In contrast, a study by Harrison et al., in 2002, showed that the risk of post-operative infection is dependent on wound contamination. HIV status was not found to be a risk factor for wound infection following operative management of closed fractures.13 The study reinforced earlier findings that asymptomatic HIV-positive patients with high energy open injuries were prone to infection compared to HIV negative.14 In contrast to this, Howard et al. showed that HIV does not necessarily increase early infection in open fractures.15 These findings were echoed by Niewoudt et al., who noted that HIV did not appear to be associated with an increased risk of deep infection or non-union in grade III open tibia fractures treated with circular external fixation.16 The influence of CD4 count on the development of infection also remains unclear. Guild et al., showed an increased infection rate in patients with a CD4 count below 300.17 All of the above-mentioned studies, however, focused on contiguous (post-operative or post-traumatic) infections. Limited data is available on the impact of HIV on haematogenous osteomyelitis.

Lavy and co-workers noted a three-fold increase in the number of septic cases treated in Malawi and speculated that this may, at least in part, have been the result of an increased seroprevalence of HIV.18 While osteomyelitis was mentioned in this report, haematogenous osteomyelitis was not specifically looked at. In 1996 Jellis reported an increase in the incidence of adult long-bone haematogenous osteomyelitis in patients with HIV and further stated that it was a common orthopaedic presentation of adults with advanced HIV disease.19

The aim of this study was to determine the prevalence of HIV infection among adult patients presenting with chronic haematogenous osteomyelitis in an attempt to investigate the possible association between HIV infection and adult chronic osteomyelitis. Intuitively, it seems reasonable to expect that an immune-compromising disease like HIV/AIDS might cause an increase in the incidence of reactivation of quiescent adult osteomyelitis, especially in patients with very low CD4 counts.

Somewhat surprisingly we found a lower prevalence of HIV infection among adult patients presenting with chronic haematogenous osteomyelitis in comparison to adult osteomyelitis from other causes (13% vs 32%, p=0.04). The prevalence of HIV infection in the contiguous group of patients was comparable to that seen in the general population of the region where the study was performed; however, in the haematogenous group it was considerably lower. In addition, the HIV-positive patient who did present with haematogenous osteomyelitis did not have

**Table II: Risk factors used to stratify the physiological status of the host**

<table>
<thead>
<tr>
<th>Major risk factors</th>
<th>Minor systemic risk factors</th>
<th>Minor local risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count &lt;350 cells/mm³</td>
<td>HIV infection</td>
<td>Poor soft tissues requiring flap</td>
</tr>
<tr>
<td>Albumin &lt;30 g/L</td>
<td>Anaemia</td>
<td>Chronic venous insufficiency</td>
</tr>
<tr>
<td>HbA1C &gt;8%</td>
<td>Smoking</td>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>Cellulitis or abscess</td>
<td>Diabetes mellitus</td>
<td>Previous radiation therapy</td>
</tr>
<tr>
<td>Malignancy at site of infection</td>
<td>Rheumatoid arthritis</td>
<td>Surgery will result in instability</td>
</tr>
<tr>
<td>Pathological fracture</td>
<td>Chronic lung disease</td>
<td>Adjacent joint stiff/arthritic</td>
</tr>
<tr>
<td></td>
<td>Chronic cardiac failure</td>
<td>Heterotopic ossification</td>
</tr>
<tr>
<td></td>
<td>Paraplegia/quadruplegia</td>
<td>Failed reconstruction elsewhere</td>
</tr>
<tr>
<td></td>
<td>Drug or substance abuse</td>
<td>Foot involvement</td>
</tr>
<tr>
<td></td>
<td>Chronic corticosteroid use</td>
<td>Pelvic involvement</td>
</tr>
<tr>
<td></td>
<td>Active tuberculosis</td>
<td>Adjacent joint involved</td>
</tr>
<tr>
<td></td>
<td>Ischaemic heart disease</td>
<td>Segmental resection of &gt;6 cm required to achieve cure</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
<td>Compliance and motivation</td>
</tr>
<tr>
<td></td>
<td>Compliance and motivation</td>
<td>Age &gt;65 years</td>
</tr>
<tr>
<td></td>
<td>Common variable immune deficiency</td>
<td></td>
</tr>
</tbody>
</table>

**Results**

A total of 149 patients met the inclusion criteria. Four patients with early post-operative infection and two patients with fungal osteomyelitis were excluded, leaving a total of 143 patients in the study group. The mean age of patients was 38 years (range 14–78; standard deviation [SD] 15.5 years). Twenty-eight per cent (n=40) of patients were found to be HIV positive with a mean CD4 count of 414 cells/mm³ (range 13–1,034; SD 132 cells/mm³). Sixty per cent (n=24) of patients were classified as A hosts, 41% (n=59) were B hosts and 44% (n=63) C hosts. Of the B hosts, nine patients were HIV-positive with a mean CD4 of 627 cells/mm³. Thirty-one (49%) of C hosts were HIV-positive, mean CD4 352 cells/mm³. 28 patients in the contiguous group (mean CD4 405 cells/mm³). The prevalence of HIV infection among patients with contiguous (post-operative or post-traumatic) infections was 29% [n=42] in 27% of cases (n=75), femur 52% (n=13), humerus, pelvis or foot in 5% (n=7), fibula or radius/ulna in 3% (n=5) and clavicle in 1% of cases. Overall, 15% (n=21) of patients were classified as A hosts, 41% (n=59) were B hosts and 44% (n=63) C hosts. Of the B hosts, nine patients were HIV-positive with a mean CD4 of 627 cells/mm³. Thirty-one (49%) of C hosts were HIV-positive, mean CD4 352 cells/mm³.

The prevalence of HIV infection among patients with contiguous (post-operative or post-traumatic) infections was 32%, in comparison to 13% in the group with reactivation of chronic haematogenous infections (p=0.04; OR 3.2; 95% CI 1.0–9.8) (Table III). In addition, there was a significant difference between the two groups in terms of the site of infection, the physiological stage of the host and the anatomic nature of the disease (Table III). Two of the four HIV patients in the haematogenous group (mean CD4 487 cells/mm³) were on antiretroviral medication compared to 12 of the 28 patients in the contiguous group (mean CD4 405 cells/mm³).
exceptionally low CD4 counts. While this study by no means provides the definitive answer, it appears that HIV infection may not necessarily be associated with the reactivation of quiescent haematogenous osteomyelitis in adults, as was initially thought.

This study has several shortcomings. Due to the retrospective nature of the study it was not possible to determine how many patients with haematogenous osteomyelitis remained asymptomatic. Thus, we were unable to compare the true prevalence of reactivation in HIV-positive and -negative patients. A long-term prospective follow-up of patients with haematogenous osteomyelitis will be required for this purpose. A further limitation is the small sample size, especially in the haematogenous group. The question therefore remains unanswered and further research in the field is warranted.

### Conclusion

The prevalence of HIV infection among patients with reactivation of chronic haematogenous osteomyelitis appeared to be lower than that seen in patients with chronic osteomyelitis from other causes, and lower than that seen in the general population in South Africa. This appears to be in contradiction to previous reports stating that HIV infection may be associated with adult chronic haematogenous osteomyelitis.

### Ethics statement

Prior to commencement of the study ethical approval was obtained from the following ethical review boards:
1. KwaZulu-Natal Department of Health (KZ_2016RP44_836)
2. Biomedical Research Ethics Committee (BREC 204/16)

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed written consent was not obtained from all patients included in the study.

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### Table III: Comparative statistics of patients with reactivation of chronic haematogenous osteomyelitis and contiguous osteomyelitis

<table>
<thead>
<tr>
<th></th>
<th>Haematogenous chronic osteomyelitis (n=31)</th>
<th>Contiguous chronic osteomyelitis (n=112)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibia</td>
<td>12 (39%)</td>
<td>63 (56%)</td>
<td>0.01**</td>
</tr>
<tr>
<td>Femur</td>
<td>15 (48%)</td>
<td>24 (21%)</td>
<td></td>
</tr>
<tr>
<td>Humerus</td>
<td>-</td>
<td>7 (6%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (13%)</td>
<td>18 (16%)</td>
<td></td>
</tr>
<tr>
<td><strong>Host staging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-host</td>
<td>13 (42%)</td>
<td>8 (7%)</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>B-host</td>
<td>10 (32%)</td>
<td>49 (44%)</td>
<td></td>
</tr>
<tr>
<td>C-host</td>
<td>8 (26%)</td>
<td>55 (49%)</td>
<td></td>
</tr>
<tr>
<td><strong>Anatomic classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>-</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>-</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>Type 3</td>
<td>26 (84%)</td>
<td>44 (39%)</td>
<td></td>
</tr>
<tr>
<td>Type 4</td>
<td>5 (16%)</td>
<td>63 (56%)</td>
<td></td>
</tr>
<tr>
<td><strong>HIV status</strong></td>
<td></td>
<td></td>
<td>0.04*</td>
</tr>
<tr>
<td>Positive</td>
<td>4 (13%)</td>
<td>36 (32%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>27 (87%)</td>
<td>76 (68%)</td>
<td></td>
</tr>
<tr>
<td><strong>CD4 count</strong></td>
<td>487 (360–646)**</td>
<td>405 (13–1 034)**</td>
<td>0.47v</td>
</tr>
</tbody>
</table>

(i) n (%); (ii) mean (range); (iii) chi-square test; (iv) Fisher’s exact test (v) t-test; (vi) CD4 count of HIV-positive patients in each group

---

### Declarations

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

### Acknowledgements

None

### Author contributions

ZS: Literature review conceptualisation, design, data collection and analysis, manuscript.
LCM: Conceptualisation, design, data collection and analysis, manuscript.

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### References


Minimally invasive CT-guided excision of osteoid osteoma and other small benign bone tumours: a single centre case series in South Africa

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Abstract

Background: The management of osteoid osteoma (OO) and other small primary benign lesions of bone has evolved over the past 50 years from open surgery with wide resection margins to less invasive surgical techniques such as image-guided intralesional excision and percutaneous radiofrequency ablation. We aim to evaluate the outcomes of patients treated with computerised tomography (CT-guided) intralesional excision and bone grafting of small benign lesions of bone.

Method: A retrospective folder review of patients treated in a large academic hospital in Cape Town, South Africa, between March 2012 and May 2016 was performed. Patient demographics, details of presentation, clinical information and outcome following treatment were analysed descriptively. Pre-operative diagnosis based on radiological examination was compared with histological diagnosis.

Result: Eleven patients (five male) with a median age of 16 years (range 5–33) were included. Pain was the most common presenting feature. A histological diagnosis of OO was confirmed in five of nine patients with a suspected diagnosis of OO pre-operatively. Of the four patients whose diagnosis changed after the procedure, the diagnoses included a benign spindle cell lesion, a benign fibrous histiocytoma, subacute osteitis and an osteochondral defect with geode cyst formation. Of the two patients where OO was not suspected pre-operatively, chondroblastoma was confirmed in one while a benign spindle cell lesion was reported in the other. Overall histological yield was thus 100%. There were no complications or repeat procedures at a median follow-up of 42 months (range 30–52 months).

Conclusion: CT-guided intralesional curettage is a safe and minimally invasive technique. This is especially useful in less accessible regions of the skeleton as it provides a means of accurately locating the lesion with minimal risk of complications and morbidity to the patient. We consider this to be the optimal method of treatment in our setting as it provides high success rates, few complications and a histological diagnosis without the need for any additional and expensive equipment.

Level of evidence: Level 4

Key words: CT guidance, osteoid osteoma, percutaneous treatment, benign bone tumours, intralesional curettage, radiofrequency ablation
Introduction

Osteoid osteoma (OO) is one of the most important primary benign bone lesions of bone, due in part to the profound pain and disability it causes patients. It is also the most common, accounting for 12% of primary benign bone tumours. Its differential diagnosis includes osteoblastoma, chondroblastoma, enchondroma and chondromyxoid fibroma as well as traumatic conditions, such as stress fracture, or infection, in the case of a Brodie’s abscess. The natural history of an OO is that of spontaneous resolution, and malignant transformation has never been described. Symptomatic relief can be gained with the regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) but side effects, particularly gastric irritation, may hamper this strategy. In refractory cases surgical excision is usually curative. This may be performed in a number of ways: either by open marginal excision or through less invasive techniques, performed under image guidance, such as direct curettage, laser photocoagulation and radiofrequency ablation with or without biopsy. Novel techniques such as magnetic resonance-guided focused ultrasound (MRgFUS) and arthroscopic excision are also currently being evaluated.

While the use of novel techniques to deal with small benign bone tumours is becoming ever more popular, the additional time and cost are not yet justified by better patient outcomes.

At our centre, computer tomography (CT) guided percutaneous curettage and bone grafting is performed as this method has a high success rate, a low number of complications, and provides a histological diagnosis without the need for costly additional equipment.

The aim of this study was to describe the surgical technique and determine the clinical outcomes of patients treated by CT-guided percutaneous curettage.

Materials and methods

Following institutional ethical approval (HREC REF: 670/2016) a retrospective folder review was performed. Included were all patients who underwent minimally invasive CT-guided intralesional excision of a primary benign bone tumour between March 2012 and May 2016. Excluded were extraosseous lesions, inadequate follow-up (less than one year), incomplete records and lesions that were malignant or located outside of bone. Patient demographics, details of presentation, clinical information and outcome following treatment were analysed. Pre-operative diagnosis based on radiological assessment was compared with histological diagnosis.

Surgical technique and aftercare

A senior surgeon performed the surgery in all cases at a single centre and all patients gave informed consent prior to surgery. Patients were admitted on the morning of surgery and discharged on the same day. Prophylactic cefazolin 1 g, or clindamycin 600 mg in the case of penicillin allergy, was administered. Anaesthesia was induced in theatre after which the patient was transferred to the radiology suite and positioned inside the CT scanner. The location of the lesion was accurately determined in the axial, sagittal and coronal planes. The entry point was planned and marked on the skin (such that the path of the wire would avoid major anatomical structures). A threaded tipped Kirschner wire (K-wire) was inserted percutaneously by a qualified radiologist under CT guidance, in a sterile manner, using an orthopaedic drill (Figures 1 and 2). The K-wire was then cut to within 3 cm of the skin and covered with a sterile dressing. The patient was then transferred back to theatre, where a full standard preparation and draping was performed. A small skin incision was made to allow a 6 mm cannulated drill bit to be passed over the K-wire and drilled down into the lesion. The K-wire was lubricated with K-Y Jelly (Reckitt Benckiser, Berkshire, UK) to prevent it from spinning with the drill bit and inadvertently advancing beyond the lesion. A long-handled curette was passed down the drill hole (after removing the K-wire) and the contents of the lesion curetted and sent for histology and microbiological culture. Fluoroscopy was used to confirm the position of the K-wire and ensure adequacy of the curettage. Allomatrix (Wright Medical, Middlesex, UK) demineralised bone matrix (DBM) calcium sulphate putty was injected into the cavity and the incision closed in a standard fashion. Postoperatively patients with lower limb lesions were kept non-weight bearing on crutches for two weeks with graduated return to full weight bearing status at six weeks. No specific rehabilitation or weight bearing protocol was prescribed. Patients had X-rays (XR) postoperatively to assess recurrence and adequacy of healing.

Statistical analysis

Due to the small cohort identified, meaningful statistical analysis was not feasible. We therefore report on descriptive statistics only.

Results

All patients presented due to limb pain and had a delay to final diagnosis. A histological diagnosis was available in all cases and there were no complications or recurrence. Four of the nine patients with suspected OO had histological diagnosis of a different benign lesion.
**Patients**

Thirteen patients were identified who had undergone CT-guided percutaneous excision of a primary bone lesion. Two patients were excluded. These included a biopsy of a metastatic renal cell carcinoma from within the muscles of the shoulder girdle and the other a biopsy of a retroperitoneal Schwannoma.

**Demographics**

Overall, there were five male patients and six female, with a median age 16 years (range 5–33). Of the five patients with an OO, three were male, the median age of whom was 19 years (range 12–20).

**Symptoms at presentation**

Localised pain was the primary presenting complaint in all patients with a median duration of 6 months (range 1–26 months). In four of the 11 (36%) patients, the pain was associated with a limp; seven of the 11 (63%) complained of night pain; and three (27%) had activity-related pain. Six (54%) patients reported pain relief with NSAID use. All five of the patients with OO complained of night pain and three of these reported transient relief of symptoms with NSAID use. One patient with a proximal tibia OO had mechanical knee symptoms including knee locking and an effusion. This patient had a delay in diagnosis of 26 months as meniscal pathology was suspected and the initial magnetic resonance image (MRI) failed to diagnose OO. These symptoms resolved following excision of the OO. There was no difference in clinical presentation between patients with OO and those with other diagnoses.

**Imaging studies**

Imaging included conventional XR (**Figure 3**), CT (**Figure 4**) and MRI (**Figure 5**). All patients had an XR initially, eight went on to have an MRI and three had a CT scan. Of the patients who had an MRI scan (n=8), three had no further imaging while five patients subsequently underwent a CT scan as the result of the MRI was inconclusive but OO was suspected. OO was accurately diagnosed in four of these CT scans.

**Location and histology**

The location of the lesions as well as the initial and final diagnoses are summarised in **Table 1**. No lesion was larger than 20 mm in diameter, with a median of 9 mm (range 4–20 mm). Microbial culture was negative in all cases. Nine patients were thought to have an OO on clinical and radiological assessment pre-operatively. In two of these patients, subacute osteitis was included in the differential diagnosis. Histological examination confirmed OO in five of these nine patients and subacute osteitis (Brodie's abscess) in one. The other three histological diagnoses were an osteochondral defect of the talus with an associated geode cyst, a benign spindle cell lesion and a benign fibrous histiocytoma.

Two patients had a primary diagnosis that did not include OO. One patient was thought to have a chondroblastoma of the calcaneus that was confirmed on biopsy while the other patient, with a lesion in the ilium adjacent to the sacroiliac joint, had a wider radiological differential diagnosis including osteoblastoma, chondroblastoma or a subchondral geode. Histology proved this to be a benign spindle cell lesion.
Outcomes and follow-up

The median follow-up time was 42 months (range 30–52 months). No patients had recurrence of symptoms, surgical complications or secondary surgical procedures. In the patients who had histologically confirmed OO (n=5), all patients had pain relief following surgery and remained symptom-free with no radiological signs of recurrence, as did five of the six patients with other diagnoses. The patient whose symptoms did not resolve had a diagnosis of an osteochondral lesion of the talus and was referred to a foot and ankle specialist for further treatment.

Discussion

The aim of this study was to present our experience with CT-guided intralesional curettage of benign bone tumours, with an emphasis on OO.

Localised pain is the most common primary presenting complaint (85% of cases) and is classically described as being worse at night and relieved by NSAIDs.18,19 Night pain was present in all of our patients with OO as well two patients with other tumour diagnoses. Six of the 11 patients reported symptomatic relief with NSAID use. Of these six, three had a final diagnosis of an OO. The natural history of OO is to resolve over time and up to 40% of patients experience long-term relief with NSAIDs.20 For this reason some authors advocate non-operative management.5 All patients in our series had failed a trial of conservative management prior to surgical intervention. As a tertiary referral centre all patients had at least one form of imaging modality prior to referral to our clinic and relieved by NSAIDs. 18,19 Night pain was present in all of our patients with OO as well two patients with other tumour diagnoses. Six of the 11 patients reported symptomatic relief with NSAID use. Of these six, three had a final diagnosis of an OO. The natural history of OO is to resolve over time and up to 40% of patients experience long-term relief with NSAIDs.20 For this reason some authors advocate non-operative management.5 All patients in our series had failed a trial of conservative management prior to surgical intervention. As a tertiary referral centre all patients had at least one form of imaging modality prior to referral to our clinic and presented to us with a differential diagnosis of OO or other small benign lesion. OO has been described mainly in young patients and is most common in the long bones of the lower limbs, especially in the metaphyseal region of the femur and tibia.16,17 We noted similar findings of age and location in our case series, but found that the clinical presentation was neither sensitive nor specific for predicting the diagnosis. Hence, we believe histological confirmation should be an essential part of the surgical management of these lesions.

The time from onset of symptoms to surgical treatment ranged from 1–25 months (median 14 months). This diagnostic delay is not unique to our setting and is due to the rarity of the condition and wide differential for limb pain in the active young patient. Cantwell describes a missed case of intra-articular OO in the hip of an 18-year-old patient where the diagnostic delay was 2.5 years due to inadequate imaging and failure to suspect the diagnosis.22 In our series a young male sportsman with a proximal tibia OO initially presented with knee pain and meniscal symptoms. An MRI failed to diagnose an OO and the presumed cause of his pain was meniscal pathology. After a failed course of conservative treatment, a repeat MRI and a CT scan diagnosed an OO that was successfully treated by the method described above. Skeletal imaging plays a major role in the diagnosis of OO. Initially plain X-rays are the modality of choice due to the relatively low cost and radiation exposure, but the diagnostic yield is far superior with CT.23,24 The potential advantage of MRI over CT is in decreased radiation exposure, particularly to the paediatric patient, but the diagnostic accuracy has been shown to be inferior.25,26 Hosalkar et al. found MRI only had a 19% (7/36) accuracy in diagnosing OO, while all lesions in this series were accurately diagnosed pre-operatively on fine cut CT imaging.28 The use of gadolinium enhancement in MRI scanning may improve diagnostic accuracy but this increases cost and it has not been shown to be superior to CT.29 In our series, CT was more accurate in diagnosing OO; four of the five patients with an OO had an inconclusive MRI but went on to have a CT that accurately diagnosed OO. Microbiological culture was negative in all patients, despite one patient having subacute osteitis on histological examination. Negative cultures in subacute osteitis are well described.30

The role of surgical management and different techniques

The most common indication for surgery is failed medical management.17 Other indications include prevention of growth deformity in intra-articular or juxta-epiphyseal lesions and the need for histological confirmation of the diagnosis.18 While some authors advocate treatment without biopsy,3 we believe it is an essential part of management. Surgical options range from open marginal resection to less invasive image-guided techniques such as radiofrequency ablation (RFA), laser photocoagulation and intralesional curettage. These are summarised in Table II.

Marginal resection is associated with prolonged surgical time, local morbidity, fracture in up to 4.5% of cases,31 and a recurrence rate of up to 9%.32 Less invasive procedures are therefore preferred.33 Open intralesional excision is less invasive, results in less local morbidity and has a more rapid recovery.31,32,34 Intraoperative imaging can be augmented with tetracycline labelling

### Table I: Summary of patient demographics, lesion location and diagnoses

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Location</th>
<th>Duration of symptoms (months)</th>
<th>Provisional diagnosis</th>
<th>Histological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>Male</td>
<td>Calcaneus</td>
<td>3</td>
<td>Chondroblastoma</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>Female</td>
<td>Proximal femur</td>
<td>26</td>
<td>Osteoid osteoma</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>Male</td>
<td>Proximal tibia</td>
<td>6</td>
<td>Osteoid osteoma</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>Female</td>
<td>Tibia</td>
<td>13</td>
<td>Osteoid osteoma</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>Male</td>
<td>Proximal tibia</td>
<td>18</td>
<td>Osteoid osteoma</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>Female</td>
<td>Calcaneus</td>
<td>3</td>
<td>Osteoid osteoma</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>Male</td>
<td>Distal femur</td>
<td>6</td>
<td>Osteoid osteoma or subacute osteitis</td>
</tr>
<tr>
<td>8</td>
<td>19</td>
<td>Female</td>
<td>Proximal femur</td>
<td>3</td>
<td>Osteoid osteoma</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>Female</td>
<td>Pelvis</td>
<td>1</td>
<td>Osteoid osteoma, osteoblastoma or osteitis</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>Female</td>
<td>Pelvis</td>
<td>3</td>
<td>Osteoblastoma, chondroblastoma or a subchondral geode cyst</td>
</tr>
<tr>
<td>11</td>
<td>12</td>
<td>Male</td>
<td>Tibia</td>
<td>26</td>
<td>Osteoid osteoma</td>
</tr>
</tbody>
</table>
and intra-operative scintigraphy to improve accuracy where these technologies are available. There is no consensus on the benefit of adjuncts (liquid nitrogen, ethanol or PMMA) and there is ample evidence that simply removing the nidus is sufficient to bring about symptomatic relief. The use of CT to accurately localise the nidus allows for a minimally invasive percutaneous biopsy and RFA. Histological yield ranges from 17–100% (mean 55%) with the combined technique, comprising biopsy and RFA. Histological yield is reported between 50 and 100%. Importantly, histological specimen is not usually sent.

Overall the rate of complications and cure for the percutaneous techniques is very similar. The possible shorter surgical time of drill curettage may result in more cost-effective economics is increasing at an alarming rate and the importance of cost containment cannot be over emphasised. Moser et al. found the cost of consumables for Laser photo coagulation and RFA to be equivalent, while Hoffmann et al. found RFA, which

Table II: Descriptions of interventional techniques for the treatment of benign lesions of bone

<table>
<thead>
<tr>
<th>Description</th>
<th>Technique</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide marginal resection ('en-bloc')</td>
<td>Extensive open surgical procedure; lesion excised with margin of normal bone</td>
<td>No additional equipment needed; technically relatively simple</td>
<td>Large soft tissue dissection; moderate bone defect; longer recovery time; fracture risk</td>
</tr>
<tr>
<td>Open intralesional resection ('burr-down')</td>
<td>Open procedure; nidus directly removed without any margin of bone under image guidance</td>
<td>Less soft tissue dissection and minimal bone excised</td>
<td>Difficulty in locating lesion may require the use of adjuncts; recurrence risk</td>
</tr>
<tr>
<td>Percutaneous CT-guided intralesional curettage</td>
<td>Guide wire placed under CT; nidus removed by indirect means under fluoroscopic guidance</td>
<td>Percutaneous procedure; minimal soft tissue trauma; low fracture risk; histology specimen</td>
<td>Requires radiology services to place guide wire</td>
</tr>
<tr>
<td>Percutaneous CT-guided RFA</td>
<td>CT-guided wire placement followed by RFA; nidus ablated by thermal necrosis</td>
<td>Percutaneous procedure; minimal soft tissue trauma</td>
<td>Requires radiology services to place guide wire; lower histological yield; additional equipment needed including RF generator and single use probes</td>
</tr>
<tr>
<td>Percutaneous CT (or MRI)-guided laser photocoagulation</td>
<td>As for RFA but uses laser to ablate lesion</td>
<td>Potentially less radiation than RFA (can be performed under MRI guidance)</td>
<td>Increased cost with no proven benefit over RFA</td>
</tr>
<tr>
<td>Arthroscopic excision</td>
<td>Lesion excised under arthroscopic visualisation with a burr</td>
<td>A minimally invasive technique</td>
<td>Requires specialised skill and surgical equipment; only suitable for intra-articular lesions</td>
</tr>
<tr>
<td>Magnetic resonance-guided focused ultrasound</td>
<td>MRI-guided focused US causes heat necrosis of the lesion</td>
<td>A non-invasive, transcutaneous technique</td>
<td>Requires specialised equipment, not readily available in most centres; as for surgical procedures, regional or general anaesthesia is required; no histology</td>
</tr>
</tbody>
</table>

Table III: List of complications associated with RF ablation (n=1 227)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary failure</td>
<td>61 (5%)</td>
</tr>
<tr>
<td>Skin burn</td>
<td>12</td>
</tr>
<tr>
<td>Muscle burn</td>
<td>6</td>
</tr>
<tr>
<td>Nerve injury</td>
<td>3</td>
</tr>
<tr>
<td>Fracture</td>
<td>2</td>
</tr>
<tr>
<td>Technical difficulty</td>
<td>5</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
</tr>
<tr>
<td>Anaesthetic complication</td>
<td>3</td>
</tr>
<tr>
<td>Delayed healing</td>
<td>2</td>
</tr>
</tbody>
</table>

Cost implications of different treatment modalities

The cost of health care in both developed and developing economies is increasing at an alarming rate and the importance of cost containment cannot be over emphasised. Moser et al. found the cost of consumables for Laser photo coagulation and RFA to be equivalent, while Hoffmann et al. found RFA, which
was performed as an outpatient procedure, to be the most cost effective with a base price of $6 583.00 USD (R81 359.00). Open resection $13 826.00 USD (R170 876.00), intrallesional resection $10 857.00 USD (R13 418.00) and CT-guided drill curettage $8 589.00 USD (R106 150.00) were all more expensive. However these results from Germany cannot be extrapolated to other regions as in different economies certain elements of the treatment package may have different financial weightings. For example, a procedure which takes less theatre time but uses more expensive consumables may be cost effective in one country while being unaffordable in another. Also of note is that the cost of CT, MRI, fluoroscopy, theatre time, anaesthesia, hospital stay, post-operative rehabilitation and time away from work have not been assessed in the above figures and impact on the economic cost to hospital and patient.

Overall, the limitations of the study include the small, heterogeneous sample and the retrospective nature of data gathering. No specific pain or functional scores were used, and no specific statistical tests could be applied to our data. CT scan was not performed post-operatively.

Conclusion

As novel techniques to deal with small benign bone tumours are becoming ever more popular, the additional time and cost may not be justified by better patient outcomes. In our series we found these elusive lesions difficult to diagnose based purely on clinical and radiological findings. While CT scan is the imaging modality of choice, histological confirmation remains an essential part of surgical management. For the included patients, CT-guided biopsy and intrallesional curettage was a safe, effective, minimally invasive treatment option with high histological yield. Future research should focus on cost effectiveness and duration of these procedures compared to conventional techniques. Sufficiently powered multicentre trials are necessary to support recommendations for South African orthopaedic surgeons treating these lesions.

Ethics statement

Ethics approval was obtained from the University of Cape Town Human Research Ethics Committee (Ethics number HREC: 670/2016). Patient information was obtained from a prospective database at Groote Schuur and Vincent Pallotti Hospitals. The Ethics Committee approved these databases, and their reference numbers respectively are R039/2013 and R001/2015. For this study formal consent was not required.

Declaration

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

Author contributions

KH conceived of the research idea and was the primary surgeon in all cases. TH assisted with application to the departmental research committee and ethics board. TH and TSC developed the study protocol and gathered patient data. TSC, TH and MH contributed to writing up the manuscript for submission.

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References


Burden and profile of spinal pathology at a major tertiary hospital in the Western Cape, South Africa

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Abstract

Background: Spinal pathology in the Western Cape is managed at three tertiary level hospitals, including Tygerberg Hospital. The Tygerberg Hospital Orthopaedic Spinal Unit is responsible for the management of spinal pathology for the 3.4 million people in the hospital's catchment area. However, the unit's overall burden of disease and associated resource use is currently unclear.

Aim: The first aim was to investigate the overall burden and clinical profile of spinal pathology presenting to the Tygerberg Hospital Spine Unit over a one-year period. The second aim was to determine resource use associated with spine pathology admissions.

Methods: Overall burden was investigated by performing a retrospective review of all patients admitted to the Spine Unit between 1 October 2016 and 30 September 2017. Demographic and clinical data was collected, and patients were assigned to one of five spinal pathology sub-groups. Resource use was determined by length of hospital stay, waiting times, advanced imaging and theatre usage.

Results: Overall burden comprised 349 individual patients and 376 admissions, including readmissions. Trauma (51%) and infection (24%) accounted for the majority of admitted pathology with degenerative (10%), deformity (7%) and malignancy (7%) representing fewer admissions. Motor vehicle accidents were the primary mechanism of injury, accounting for 48% of spine trauma. Tuberculosis was the causative organism in 87% of spinal infections with 44% HIV co-infection. Hospital resource use was considerable with 92% of spine patients requiring advanced imaging, a median operating time of 3 h 36 min and a median hospital stay of 19 days. Infection and malignancy sub-groups had the longest waiting times for advanced imaging and theatre with a median wait of 14–16 days, accounting for approximately 62% of the typical total hospital stay.

Conclusions: The Spine Unit experienced a substantial patient burden requiring significant hospital resources. Reduced in-patient waiting times and upskilling of orthopaedic services at secondary hospitals represent key areas for health system strengthening. However, multi-sectoral strategies would be required to effectively address our high burden of largely preventable spinal pathology.

Level of evidence: Level 4

Key words: spinal pathology epidemiology, spinal trauma, spinal tuberculosis, spinal surgery
Introduction

Spinal pathology represents a wide spectrum of disease involving components of the Functional Spinal Unit and contents of the spinal canal. Typical spinal orthopaedic presentations can be broadly classified into trauma, infection, malignancy, degenerative and deformity subgroups, each of which involve a distinct diagnostic and management approach. Nevertheless, all types of spinal pathology can have major implications for functional ability and quality of life, hence access to appropriate treatment is of high importance.

In the Western Cape, specialist spinal services are only available at three tertiary level hospitals, including Tygerberg Hospital. Officially opened in 1976, Tygerberg Hospital is the largest tertiary hospital in the province and the second largest in the country with 1 384 active beds and an annual budget of R2.6 billion. Tygerberg Hospital’s Orthopaedic Spinal Unit is responsible for the management of all spinal column pathology, including acute, non-penetrating spinal cord injuries, for a population of 3.4 million within the hospital’s catchment area. However, the unit is staffed by only one permanent and one sessional consultant, a long-term fellow and two orthopaedic registrars.

Anecdotal evidence suggests that the Spine Unit manages a significant volume of patients, many of whom require advanced imaging, considerable theatre time and a lengthy hospital stay. However, this has not been formally investigated, with previous burden of disease studies focusing on specific conditions such as spinal cord injury and spinal tuberculosis (TB). It follows that the overall profile of spinal pathology presenting to a tertiary institution in South Africa and the associated burden on health system resources is currently unclear.

With this in mind, the first aim of the current study was to investigate the overall burden and clinical profile of spinal pathology presenting to the Tygerberg Hospital Spinal Unit over a one-year period, including patient demographics and human immunodeficiency virus (HIV) prevalence within each pathology subgroup. The second aim of the study was to determine the resource use associated with spinal pathology admissions, including the length of hospital stay, use of advanced radiological modalities and theatre time. It is envisaged that increased insight into the volume, distribution and resource costs of spinal pathology within our setting will help to identify areas for health system strengthening, including accurate and adequate resource allocation.

Materials and methods

Overall burden

A retrospective review was performed of all patients admitted to the Spine Unit at Tygerberg Hospital during the period 1 October 2016 to 31 September 2017. Patients were initially identified from the admission files of the Unit’s primary admitting wards, after which this list was cross-referenced with the principal investigator’s personal surgical logbook to ensure that no surgical cases were unaccounted for. All duplicate cases were identified and removed.

Demographic and clinical characteristics

Patient case records, radiological and biochemical investigations were reviewed, and clinical and demographic information collected for each patient included age, sex, residential area, region of pathology and HIV status. Patients were also assigned to one of five spinal pathology subgroups based on clinical notes: trauma, deformity, degenerative disease, infection and malignancy.

Further information pertaining to the two most prevalent subgroups, trauma and infection, was also collected. Trauma data included the mechanism of injury (MOI), presence of polytrauma, and American Spinal Injury Association (ASIA) score on admission. Among patients with infection, the causative organisms were categorised as TB or ‘other’ and Frankel grade on admission was recorded.

Resource use

To determine the resource use per patient, the length of hospital stay, use of advanced radiological investigations, total theatre time, and waiting times for surgery and for advanced imaging were recorded. Theatre time was obtained from intra-operative records of the anaesthetic start and end times as recorded by a member of the nursing team.

<table>
<thead>
<tr>
<th>Total admissions</th>
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<tbody>
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<td>Repeat admissions</td>
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<tr>
<td>Individual patients</td>
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<td>IPV</td>
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<tr>
<td>Fall</td>
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<td>Other</td>
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</table>

Figure 1. Absolute burden of patients admitted to Tygerberg Hospital Spinal Unit within a one-year period, in total and by pathology. VA = vehicle accident, IPV = inter-personal violence. *Mechanism of trauma, missing data (n=1), *Infection causative organism unknown (n=1)
Data analysis

Categorical data was presented as counts and percentages whereas continuous data was tested for normal distribution and presented as mean ± standard deviation (SD) or median and interquartile range (IQR) as appropriate. When continuous data was normally distributed within some pathology groups but not others, median (IQR) was presented for all groups. Statistical analysis was conducted using Microsoft Excel 2013 (© 2012 Microsoft Corporation, Impressa Systems, Santa Rosa, California) and Graphpad Prism (GraphPad Prism version 6.00, GraphPad Software, La Jolla, California).

Ethical considerations

The study was approved by the Human Research Ethics Committee of Stellenbosch University and by the management of Tygerberg Hospital.

Results

Overall burden and clinical profile

A total of 349 individual patients were admitted to the Spine Unit over the one-year study period (Figure 1). In addition to the initial admission, 21 (6%) patients required one re-admission and three (<1%) patients required two re-admissions, amounting to 376 admissions in total.

Trauma and infection made up the majority of admitted pathology, accounting for 75% of the overall burden (Figures 1 and 2). Among trauma admissions, a motor vehicle accident (MVA) was the primary MOI, accounting for 48% of spinal trauma, with falls contributing a further 26%. Polytrauma was noted in 39% of trauma patients with an MVA or pedestrian vehicle accident (PVA) recorded as the MOI in 65% and 24% of polytrauma cases, respectively. TB was the dominant causative organism among patients with infection, accounting for 87% of admissions in this subgroup.

Demographic and clinical characteristics

Patient clinical and demographic characteristics are shown in Table I. Overall, most spine patients were from the Cape Metro (65%) or the Cape Winelands (18%) with a much smaller contribution from the hospital’s other referral districts.

While 17% of all spine patients were confirmed HIV positive, a further 58% had an unknown HIV status. Nevertheless, there was some variation in HIV testing between subgroups with HIV status known in 86% of the infection subgroup and only 17–46% of the other subgroups. Of the 72 patients with spinal TB, 32 (44%) were HIV positive, 33 (46%) HIV negative and seven (10%) of unknown status.

Neurology was intact in 74% and 61% of spine trauma and infection patients, respectively, with only 4–5% presenting with complete paralysis. Notably, the majority (45 of 68) of patients with polytrauma presented as ASIA E.

Figure 3. Age distribution within pathology type. Error bars indicate median and IQR

Figure 4. Operating time within pathology type. Error bars indicate median and IQR

Available operating times: trauma (n=70), deformity (n=19), degenerative (n=17), infection (n=60), malignancy (n=6), total (n=172)
Resource use

Hospital resource use associated with each initial Spine Unit admission is shown in Table II. Overall, 92% of spine patients required some form of advanced imaging, with 26% receiving both a computed tomography (CT) and a magnetic resonance imaging (MRI) scan. In contrast to other subgroups, trauma patients were most likely to have an isolated CT scan (53%) and accounted for 94% of patients receiving a CT scan only. The majority of patients in the deformity, degenerative and infection subgroups received an MRI scan only (57–82%), whereas patients with malignancy required both CT and MRI imaging in 54% of cases.

Overall, 52% of spine patients received operative management, with the trauma and infection subgroups requiring surgery in 41% and 78% of patients, respectively (Table II). Although patients with malignancy utilised the largest percentage of combined imaging out of any subgroup while admitted to the unit, only 25% underwent surgery. Of the 346 patients for whom operative data was available, the median (IQR) operating time was 3 h 36 min (1 h 48 min to 5 h 27 min). However operative time varied by subgroup with the shortest median (IQR) operative times recorded for malignancy (1 h 33 min, 1 h 09 min to 2 h 05 min) and infection (1 h 43 min, 1 h 20 min to 3 h 17 min), and the longest for deformity (7 h 06 min, 6 h 18 min to 8h 18 min) (Figure 4).

Median hospital stay varied by pathology, with the degenerative subgroup showing the shortest median stay (eight days) and the deformity subgroup the longest (38 days). Among patients with infection and malignancy, there was a median 14–16 day waiting time between admission and surgery, of which a median of 8–10 days was spent waiting for an MRI scan. It follows that waiting time for MRI and surgery typically accounted for more than 50% of the median total hospital stay of 23–25 days for these subgroups.

While the majority of patients from other subgroups were discharged home, 79% of patients with malignancy were transferred to another department within Tygerberg Hospital. Furthermore 17% of patient with infection were discharged to the Western Cape Rehabilitation Centre (WCRC), representing the most common discharge pathway for TB spine patients with neurological fallout. Only 3% of patients required referral to the Acute Spinal Cord Injury (ASCI) Unit at Groote Schuur Hospital with a further 3% recorded as ‘Other’ discharge pathways such as deaths, patient refusal of hospital treatment and absconsions.

Discussion

Burden and clinical profile

The first finding of the study was that the Orthopaedic Spinal Unit at Tygerberg Hospital experienced a substantial patient burden over the one-year study period, including 349 individual patients and 376 separate admissions. The clinical profile of spine patients was dominated by trauma and infection, with these subgroups accounting for 51% and 24% of all spine pathology, respectively.

Spinal orthopaedic surgery is a highly specialised branch of Orthopaedics and its scope of practice in our centre is not limited...
traffic accidents accounted for only 23% of all spine fractures by age or pathology type. Our varied clinical profile supports this, especially if one considers the admission of 29 paediatric patients which in itself is a significant burden given the added demands of this population group. The discipline is also predominantly consultant-driven with regard to decision-making and surgical management and includes the teaching of registrars and medical students. The high burden of spinal pathology in the state sector lacks adequate specialist cover and this is made even more apparent when compared to the private healthcare sector; a discrepancy that could possibly be explained by an increase in MVAs due to an increased number of individuals with unknown status (10% vs 16%). More importantly, the current HIV prevalence was approximately four times the estimated national HIV prevalence of 12.6% and almost certainly higher. Within the Western Cape, the Cape Metro is the district with the highest absolute burden of TB, and injuries were purported to account for injuries as South Africa.

The majority (60.5%) of spine trauma was caused by road traffic collisions, with 80% due to MVAs and the remainder to PVAs. The majority of MVA-related trauma illustrates the high-energy, acceleration/deceleration mechanisms required for spinal pathology. In contrast, a previous multicentre study assessing the burden of spine fractures in India reported that falls were the primary cause of injury in 72% of the patient group. Furthermore, traffic accidents accounted for only 23% of all spine fractures despite India having twice as many reported non-fatal road traffic injuries as South Africa. This contrast suggests that MVAs within our setting are particularly severe, a premise supported by a 2016 report ranking the Western Cape as the province with the third highest road traffic collision fatalities. Of concern is that causal analysis of fatal crashes shows that 74% are due to human factors, meaning that this massive burden is largely preventable.

While the second largest subgroup of spinal pathology was broadly described as infection, 87% of these patients were individuals with spinal TB. It is well established that the Western Cape has one of the highest burdens of TB worldwide, with a reported incidence of 681 cases per 100 000 and a true incidence that is almost certainly higher. While the Western Cape has one of the highest burdens of TB worldwide, a reported incidence of 681 cases per 100 000 and a true incidence that is almost certainly higher. Within the Western Cape, the Cape Metro is the district with the highest absolute burden of TB and this was also the district from which the majority (77%) of our spinal infection patients presented. A higher burden of spinal TB in urban areas is in keeping with previous findings from KwaZulu-Natal and is likely explained by adverse living conditions.

Another well-known risk factor for TB is HIV infection and in the current study, 44% of patients with spinal TB were HIV-infected with a further 10% of unknown HIV status. This HIV prevalence is approximately twice as high as the 20% HIV prevalence reported among patients with spinal TB treated at Groote Schuur Hospital, a discrepancy that could possibly be explained by an increase in HIV prevalence in the Western Cape between the study periods (2013–2014 vs 2016–2017), more areas with high HIV prevalence within the Tygerberg catchment area, and differences in the number of individuals with unknown status (10% vs 16%). More importantly, the current HIV prevalence was approximately four times the estimated national HIV prevalence of 12.6% and almost
seven times the HIV prevalence in the Western Cape. While this appears to suggest an association between HIV-infection and spinal TB, evidence from prospective studies is required to confirm this link.

When considering that trauma and infection account for 75% of the burden on spine services at Tygerberg Hospital, it is pertinent to note that these pathology types are to some extent preventable. For example, stricter road traffic laws and harsher penalties for infringements may help to reduce the incidence of high velocity MVAs in the province, and ongoing efforts to reduce TB transmission may reduce the incidence of spinal TB. When excluding spine pathology due to MVAs, PVAs, inter-personal violence and spinal TB, the current patient burden is reduced by 56% from 349 to 153 patients – highlighting the extent of the preventable burden. While such drastic reductions are unrealistic, the current study could serve as a useful baseline with which to audit relevant societal interventions in the future.

Resource use

The second finding of the current study was that spine pathology was a significant consumer of hospital resources with 92% of patients requiring advanced imaging, a median operating time of 3 h 36 min and a median hospital stay of 19 days. While relatively high resource consumption for managing spine pathology may be well known anecdotally, to our knowledge the current study is one of the first to formally quantify this.

High utilisation of key resources such as scanners, operating theatres and hospital beds has implications not only for hospital services but also on the expenses incurred. For example, according to current cash prices in the private sector, the average cost of a regional spinal CT and MRI is R3 600 and R6 400, respectively.

Using the aforementioned estimates, the total cost of diagnostic imaging for isolated CTs in 53% of the trauma subgroup was R342 000. The infection subgroup required the greatest number of isolated MRIs due to the modality’s value with management, and incurred a total cost of R1 305 600 for 24% of all spine patients. Exact costing for imaging modalities in the state sector was difficult, it is inferred that further training and employment of sub-specialists will improve service delivery and lower overall costs, especially when faced with the high burden of spinal pathology demonstrated in our study.

Conclusion

Our study is the first to describe admissions to a tertiary spinal unit in the South African setting and demonstrated a large patient burden and a clinical profile dominated by preventable pathologies. Our study is the first to describe admissions to a tertiary spinal unit in the South African setting and demonstrated a large patient burden and a clinical profile dominated by preventable pathologies. Future research could focus on the effectiveness of such strategies on the burden, clinical profile and resource use associated with spinal pathology.

Ethics statement

The study was approved by the Human Research Ethics Committee of Stellenbosch University and by the management of Tygerberg Hospital.

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.
amendments or comparable ethical standards. A waiver of informed consent was granted for this retrospective review.

Declaration
The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

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Author contributions
SM contributed to the original study concept, proposal write-up, data collection and analysis, and final article write-up.
TM contributed to the original study concept, data analysis, and assisted with the article and proposal write-up.
JD contributed to the study design, layout and final article concepts.

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References
Incidence and risk factors for extended post-operative length of stay following primary hip arthroplasty in a South African setting

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Abstract

Background: This study sought to determine the incidence of extended post-operative length of stay (EPLoS) and its associated risk factors in South African primary hip arthroplasty patients.

Methods: This was a retrospective chart review study of 185 adults who underwent primary hip arthroplasty at a quaternary South African hospital. Data related to patient, clinical, and surgical characteristics were collected. Post-operative length of stay was calculated as the time (in days) between the dates of surgery and discharge from hospital. We defined EPLoS as any length of stay ≥75th percentile obtained for the entire study population. Data were analysed using univariate and multivariate statistical methods.

Results: The incidence of EPLoS was 28.1% (95% confidence interval – CI: 22.1–35.0%). Risk factors for EPLoS included: female sex (odds ratio – OR: 4.63, 95% CI: 1.74–12.34; p=0.002), patient’s maximum walking distance <100 m (OR: 3.05, 95% CI: 1.05–8.89; p=0.041) and extended duration of surgery (OR: 3.62, 95% CI: 1.31–10.01; p=0.013).

Conclusion: We provide a report of EPLoS and several associated risk factors in South African primary hip arthroplasty patients.

Level of evidence: Level 4

Key words: primary hip arthroplasty, primary hip replacement, South Africa, extended length of stay, risk factors
Introduction

Increased global life expectancy has been linked to a higher burden of musculoskeletal conditions, including hip fracture and osteoarthritis. Untreated musculoskeletal conditions impact quality of life in afflicted patients and also have adverse consequences on healthcare expenditure and resource utilisation. These conditions would therefore have public health significance in resource-limited settings. Aside from non-communicable aetiologies, the global HIV epidemic has also been linked to the growing prevalence of orthopaedic disorders. Conservative medical therapy might not be effective in a large proportion of patients afflicted with orthopaedic hip conditions. Surgical intervention remains the only viable management option in these patients. The effectiveness of primary hip arthroplasty in reversing pain and loss of function associated with orthopaedic hip conditions is well described. Utilisation of primary hip arthroplasty as a surgical intervention for orthopaedic hip conditions has increased substantially over the past two to three decades, with this procedure now considered among the most common surgical procedures performed worldwide.

A survey of orthopaedic surgeon members belonging to the South African Orthopaedic Association reported that each member in the country performed up to 43 hip arthroplasties each year. In addition, a lack of surgical expertise and other essential resources in surrounding countries has resulted in a number of patients from these countries being referred to South African hospitals for the procedure. In response to the increasing demand for primary hip arthroplasty, it is possible that many South African orthopaedic surgery units will in future adopt accelerated post-operative care pathways, in which the length of inpatient stay (and subsequent expenditure and resource utilisation for each patient) following surgery is reduced. An understanding of which patient, clinical, and surgical characteristics are associated with extended post-operative length of stay (EPLoS) in South African primary hip arthroplasty patients would have important future implications for the development of fast-track or accelerated surgical and recovery protocols implemented at orthopaedic surgery units in the country.

Therefore, the objectives of this study were to:
1. Determine the incidence of EPLoS in a sample of South African primary hip arthroplasty patients
2. Determine which patient, clinical, and surgical characteristics are associated with EPLoS in a sample of South African primary hip arthroplasty patients.

Materials and methods

Study design, study setting, and study population

This was a retrospective chart review study involving consecutive adult patients who were admitted for primary hip arthroplasty through a dedicated arthroplasty unit at a quaternary level hospital in KwaZulu-Natal, South Africa, between 23 September 2014 and 28 July 2016. Inclusion/exclusion criteria for this study are presented in Table I. Potential participants were identified from theatre lists during the specified study period.

Data collection

The medical records of all patients included in this study were reviewed and data related to various patient (demographics), clinical (comorbidities, presenting diagnosis, Thomas test with fixed flexion deformity [FFD], etc.), and surgical characteristics (nature of surgery, anaesthesia, surgical approach, duration of surgery, and peri-operative blood transfusion) were collected using case report forms. We also collected data related to the occurrence of serious peri-operative complications, which we defined as a grade III or above peri-operative complication when using the Clavien-Dindo classification (includes: organ failure, critical care admission, re-operation, and mortality). Post-operative length of stay was calculated as the time (days) between the date of a patient’s operation and the date that the patient was discharged from hospital.

The study outcome was EPLoS. This was defined as a post-operative length of stay ≥75th percentile calculated for the entire study population. This definition of EPLoS has been used in similar surgical studies conducted in overseas settings. Data were transferred from the case report forms to a Microsoft Excel® spreadsheet in preparation for analysis.

Data analysis

The median length of stay for the study population was calculated and is presented with an interquartile range. The incidence of EPLoS in this study was calculated using conventional epidemiological methods. The incidence of EPLoS in this study is presented as a percentage with 95% confidence intervals (95% CI). Potential associations between various patient, clinical, and surgical characteristics and EPLoS were investigated using univariate (χ² test, or Fisher’s exact test) and multivariate (binary logistic regression) statistical methods. Results for the univariate statistical analysis are presented as frequencies and percentages. Characteristics with p<0.100 in the univariate analysis were selected for inclusion in the multivariate statistical analysis. This purposeful selection of variables for inclusion in the multivariate analysis was done to obtain the most parsimonious model possible. Model fit was assessed using a Hosmer-Lemeshow test. Results for the multivariable statistical analysis are presented as odds ratios (OR) with 95% CI. A p-value of <0.050 was considered to be a statistically significant result. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM Corp, USA).

Results

Derivation of study population and incidence of EPLoS

The derivation of the study population and the incidence of EPLoS in this study is shown in Figure 1. Following the application of our study inclusion and exclusion criteria, our final study population consisted of 185 adult patients who underwent primary hip arthroplasty. The median post-operative length of stay for the study population was 5.0 days (interquartile range: 3.0–7.0 days). The 75th percentile for the study population post-operative length of...
Results of the univariate statistical analysis

The results of the univariate statistical analysis are also shown in Table II. The proportions of several characteristics were statistically similar (p>0.050) between patients who experienced EPLoS and patients who did not experience EPLoS. These characteristics included: elderly age (p=0.130), American Society of Anesthesiologists Score (p=0.306), current smoker (p=0.061), cardiovascular disease (p=0.999), chronic obstructive pulmonary disease (p=0.327), HIV (p=0.764), diabetes (p=0.999), anaemia (p=0.970), obesity (p=0.807), hypertension (p=0.056), mobilisation with an assistive device (p=0.937), VAS (p=0.774), urgent/emergent surgery (p=0.560), general anaesthesia (p=0.739), and posterior surgical approach to the hip (p=0.216). The proportions of the remaining characteristics were statistically different (p<0.050) between patients who experienced EPLoS and patients who did not experience EPLoS. These characteristics included: sex (p=0.001), presenting diagnosis (p=0.011), FFD (p<0.011), patient’s maximum walking distance (p=0.009), extended duration of surgery (p=0.003), peri-operative blood transfusion (p=0.001), and serious peri-operative complications (p=0.023). We were unable to compute statistics for the characteristic ‘renal impairment’, as we found that no patients in our study population had this characteristic.

Results of the multivariable statistical analysis

The results of the multivariable statistical analysis are shown in Table III. Only nine of the characteristics investigated in the univariate analysis met the criteria of p<0.100 for inclusion in the multivariable analysis. These characteristics were sex, being a current smoker, hypertension, presenting diagnosis, FFD, patient’s maximum walking distance, extended duration of surgery, peri-operative blood transfusion, and serious peri-operative complications. Of these characteristics, only three were found to be independently associated with EPLoS. These characteristics were female sex (when compared with males, OR: 4.63, 95% CI: 1.74–12.34; p=0.002), patient’s maximum walking distance <100 m (when compared with the reference of walking distance ≥100 m, OR: 3.05, 95% CI: 1.05–8.89; p=0.041), and extended duration of surgery (when compared with surgery duration ≥75th percentile obtained for the entire study population, OR: 3.62, 95% CI: 1.74–12.34; p=0.002).

Discussion

The median post-operative length of stay in our South African study population was much shorter than that reported for British, American, and Pakistani patient populations undergoing primary hip arthroplasty (median of five days in our study population).
**Table II: Distribution of patient/clinical characteristics in the study population and results of the univariate statistical analysis**

<table>
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<th>Sub-category</th>
<th>All patients (N=185)</th>
<th>No EPLoS (n=133)</th>
<th>EPLoS (n=52)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age &gt;65 years old</td>
<td>Yes</td>
<td>43 (23.2)</td>
<td>27 (20.3)</td>
<td>16 (30.8)</td>
<td>0.130</td>
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<tr>
<td></td>
<td>No</td>
<td>142 (76.8)</td>
<td>106 (79.7)</td>
<td>36 (69.2)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>102 (55.1)</td>
<td>60 (45.1)</td>
<td>42 (80.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>83 (44.9)</td>
<td>73 (54.9)</td>
<td>10 (19.2)</td>
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</tr>
<tr>
<td>ASA score ≥3</td>
<td>Yes</td>
<td>71 (38.4)</td>
<td>48 (36.1)</td>
<td>23 (44.2)</td>
<td>0.306</td>
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<tr>
<td></td>
<td>No</td>
<td>114 (61.6)</td>
<td>85 (63.9)</td>
<td>29 (55.8)</td>
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</tr>
<tr>
<td>Current smoker</td>
<td>Yes</td>
<td>42 (22.7)</td>
<td>35 (26.3)</td>
<td>7 (13.5)</td>
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<tr>
<td></td>
<td>No</td>
<td>143 (77.3)</td>
<td>98 (73.7)</td>
<td>45 (86.5)</td>
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<tr>
<td>Cardiovascular disease</td>
<td>Yes</td>
<td>10 (5.4)</td>
<td>7 (5.3)</td>
<td>3 (5.8)</td>
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<tr>
<td></td>
<td>No</td>
<td>175 (94.6)</td>
<td>126 (94.7)</td>
<td>49 (94.2)</td>
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<tr>
<td>COPD</td>
<td>Yes</td>
<td>21 (11.4)</td>
<td>17 (12.8)</td>
<td>4 (7.7)</td>
<td>0.327</td>
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<tr>
<td></td>
<td>No</td>
<td>164 (88.6)</td>
<td>116 (87.2)</td>
<td>48 (92.3)</td>
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<tr>
<td>HIV</td>
<td>Yes</td>
<td>40 (21.6)</td>
<td>105 (78.9)</td>
<td>40 (76.9)</td>
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<td>No</td>
<td>145 (78.4)</td>
<td>28 (21.1)</td>
<td>12 (23.1)</td>
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<tr>
<td>Diabetes</td>
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<td>17 (9.2)</td>
<td>12 (9.0)</td>
<td>5 (9.6)</td>
<td>0.999</td>
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<tr>
<td></td>
<td>No</td>
<td>168 (90.8)</td>
<td>121 (91.0)</td>
<td>47 (90.4)</td>
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<tr>
<td>Renal impairment</td>
<td>Yes</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<td>185 (100.0)</td>
<td>133 (100.0)</td>
<td>52 (100.0)</td>
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<tr>
<td>Anaemia</td>
<td>Yes</td>
<td>53 (28.6)</td>
<td>38 (28.6)</td>
<td>15 (28.8)</td>
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<td>No</td>
<td>132 (71.4)</td>
<td>95 (71.4)</td>
<td>37 (71.2)</td>
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<tr>
<td>Obesity</td>
<td>CNBE</td>
<td>11 (5.9)</td>
<td>7 (5.3)</td>
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</tr>
<tr>
<td></td>
<td>Yes</td>
<td>84 (45.5)</td>
<td>61 (45.8)</td>
<td>23 (44.2)</td>
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</tr>
<tr>
<td></td>
<td>No</td>
<td>90 (48.6)</td>
<td>65 (48.9)</td>
<td>25 (48.1)</td>
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</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>86 (46.5)</td>
<td>56 (42.1)</td>
<td>30 (57.7)</td>
<td>0.056</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>99 (53.5)</td>
<td>77 (57.9)</td>
<td>22 (42.3)</td>
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</tr>
<tr>
<td>Presenting diagnosis</td>
<td>Other</td>
<td>44 (23.8)</td>
<td>25 (18.8)</td>
<td>19 (36.6)</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>Osteonecrosis</td>
<td>61 (33.0)</td>
<td>51 (38.3)</td>
<td>10 (19.2)</td>
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</tr>
<tr>
<td></td>
<td>Osteoarthritis</td>
<td>80 (43.2)</td>
<td>57 (42.9)</td>
<td>23 (44.2)</td>
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</tr>
<tr>
<td>FFD &gt;30 degrees</td>
<td>CNBE</td>
<td>47 (25.4)</td>
<td>26 (19.6)</td>
<td>21 (40.3)</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>25 (13.5)</td>
<td>18 (13.5)</td>
<td>7 (13.5)</td>
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</tr>
<tr>
<td></td>
<td>No</td>
<td>113 (61.1)</td>
<td>89 (66.9)</td>
<td>24 (46.2)</td>
<td></td>
</tr>
<tr>
<td>Mobilises with assistive device</td>
<td>Yes</td>
<td>138 (74.6)</td>
<td>99 (74.4)</td>
<td>39 (75.0)</td>
<td>0.937</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>47 (25.4)</td>
<td>34 (25.6)</td>
<td>13 (25.0)</td>
<td></td>
</tr>
<tr>
<td>VAS ≥7</td>
<td>CNBE</td>
<td>63 (34.1)</td>
<td>47 (35.3)</td>
<td>16 (30.8)</td>
<td>0.774</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>99 (53.5)</td>
<td>69 (51.9)</td>
<td>30 (57.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>22 (12.4)</td>
<td>17 (12.8)</td>
<td>6 (11.5)</td>
<td></td>
</tr>
</tbody>
</table>
### Table III: Results of the multivariate statistical analysis*

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Sub-category</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>4.63 (1.74–12.34)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Current smoker</td>
<td>Yes</td>
<td>1.15 (0.36–3.66)</td>
<td>0.817</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>1.36 (0.59–3.11)</td>
<td>0.470</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Presenting diagnosis</td>
<td>Other</td>
<td>2.25 (0.83–6.13)</td>
<td>0.113</td>
</tr>
<tr>
<td></td>
<td>Osteonecrosis</td>
<td>0.70 (0.24–2.01)</td>
<td>0.507</td>
</tr>
<tr>
<td></td>
<td>Osteoarthritis</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>FFD &gt;30 degrees</td>
<td>CNBE</td>
<td>4.80 (1.72–13.34)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.52 (0.14–1.91)</td>
<td>0.326</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Walking distance &lt;100 m</td>
<td>CNBE</td>
<td>0.48 (0.15–1.53)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3.05 (1.05–8.89)</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Extended duration of surgery</td>
<td>Yes</td>
<td>3.62 (1.31–10.01)</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Peri-operative blood transfusion</td>
<td>Yes</td>
<td>2.35 (0.80–6.88)</td>
<td>0.120</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Peri-operative complication</td>
<td>Yes</td>
<td>11.77 (0.95–145.54)</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Reference</td>
<td>-</td>
</tr>
</tbody>
</table>

*p<0.050 was considered a statistically significant result.

*Results expressed as frequencies (%).

**Results adjusted for confounders. Only characteristics with p<0.100 in the univariate statistical analysis included in the multivariable statistical analysis.

**OR: odds ratio; CI: confidence interval; FFD: fixed flexion deformity; CNBE: could not be established**
versus seven to eight days in the other primary hip arthroplasty populations). South Africa is severely impacted by high levels of non-communicable disease, trauma/injury, and HIV infection, all of which are associated with the development of musculoskeletal/orthopaedic disease. This has resulted in a growing demand for hip arthroplasty in the country. However there are staffing and economic challenges in running orthopaedic surgical units in the public sector, and the availability of beds in these public hospitals might also be a concern. In order to cope with the higher demand for hip arthroplasty, some hospitals are beginning to implement fast-track protocols which are aimed at reducing post-operative length of stay while minimising the rate of post-discharge complications in suitable patients who undergo the surgical procedure. This might possibly explain the difference in median post-operative length of stay following primary hip arthroplasty between South African and overseas populations. With regard to EPLoS following hip arthroplasty, the literature is scant. However, there is one American study which reported EPLoS in this surgical population. In that study, the 75th percentile for the population post-operative length of stay was 14.0 days, which is twice that reported for our study. Furthermore, one-third of the American study population experienced EPLoS. As with our findings for median post-operative length of stay, the discrepancy in EPLoS between the American study population and our South African study population must be viewed in the context of a growing demand for hip arthroplasty in South Africa and the disproportionate availability of healthcare resources between South African and American settings.

We found statistically significant univariate associations between several characteristics (including: sex, presenting diagnosis, FFD, patient's maximum walking distance, extended duration of surgery, peri-operative blood transfusion, and serious post-operative complications). These findings are not unique to our study. Other overseas studies have reported univariate statistical associations between these/similar characteristics and post-operative length of stay in hip arthroplasty patients. We found three characteristics to be independently associated with EPLoS (including: sex, patient's maximum walking distance and extended duration of surgery). Female sex was found to be associated with an almost five-fold increase in the risk of experiencing EPLoS following primary hip arthroplasty. Abbas et al., reported an almost two-fold increase in the risk of EPLoS for women undergoing hip arthroplasty in a Pakistani setting. Dall et al., also reported a multivariate statistical association (without describing the magnitude of risk) between female sex and longer post-operative length of stay a British hip arthroplasty population. Therefore, our findings for female sex appear, in general, to be in agreement with the published literature. However, the difference in the magnitude of odds ratios for female sex obtained in our study and the study of Abbas et al. requires further investigation. The characteristics of patient's maximum walking distance have not been specifically investigated as potential risk factors for EPLoS following hip arthroplasty in the published literature. However, these characteristics are components of the pre-operative Harris Hip Score, which has been shown by Dall et al., to be associated with length of stay following hip arthroplasty. Specifically, these characteristics appear to be associated with mobility and functional status in patients with hip conditions. Therefore, our findings highlight the potential importance of pre-operative functional status and ambulation on the post-operative recovery period in South African primary hip arthroplasty patients. Lastly, we found extended duration of surgery to be associated with an almost four-fold higher risk of experiencing EPLoS. This is somewhat in agreement with the British study of Foote et al., who also report extended duration of surgery to be independently associated with a higher risk of EPLoS. However, as with the patients’ sex, there appears to be a difference in the magnitude of odds ratios for surgery duration between our study and the study of Foote and colleagues. Attempts to should be made to reduce the duration of hip arthroplasty in our setting, possibly through the application of benchmarks and optimisation of surgical technique.

The risk factors identified in our study can be incorporated into future risk stratification systems for EPLoS in South African orthopaedic units. Similar risk stratification systems based on identified risk factors for EPLoS following primary hip arthroplasty have been proposed by Abbas et al., and Foote et al. These risk stratification systems are required to be developed and validated for performance in a separate surgical cohort. This step is beyond the scope of the dataset used in our study and requires further research.

There were several characteristics which were not found to be associated with EPLoS during the univariate statistical analysis, or following inclusion in the multivariable statistical analysis. There are two explanations for the lack of statistical association between these characteristics and EPLoS in our study. First, it might be possible that these characteristics, while identified as risk factors in overseas settings, are genuinely not associated with EPLoS in South African hip arthroplasty patients. Discordance in clinical risk factors between overseas/South African surgical populations and other post-operative outcomes has been described elsewhere. It might be worthwhile to involve overseas collaborators with access to overseas patient data in future research such that valid comparisons of risk factors between our settings can be made. Secondly, it is possible that a larger sample size than 185 patients would be required to investigate the impact of these characteristics on EPLoS. A potential solution to this would be a collaborative study involving as many hospitals which offer orthopaedic surgical services as possible.

Our study had several strengths. Our study is, to the best of our knowledge, the only South African study which specifically investigates EPLoS following primary hip arthroplasty. Another strength of our study is that we included data on HIV infection in our statistical analyses. This is important as the prevalence of HIV is usually much lower in American and British populations, and so our study provides important information on the impact of this characteristic in settings with a high burden of HIV infection. The final strength of our study is that while our sample size appeared modest, it still allowed for us to perform a multivariable statistical analysis to determine independent risk factors for EPLoS without any serious violation of statistical rules of thumb. Our study also had several limitations. First, as this study was conducted at a single, dedicated arthroplasty unit in a quaternary level hospital with standardised pre- and post-operative protocols in place, it might be argued that our study findings lack generalisability. As for our solution for the challenge related to the lack of statistical association between several characteristics and EPLoS, we recommend that collaborative studies involving hospitals at various levels of service delivery are conducted to determine the generalisability of our study findings. In addition, we were unable to investigate the impact of the Harris Hip Score in our study due to poor documentation of this characteristic in the patient medical records. We did, however, find that components of the Harris Hip Score were statistically associated with EPLoS, and it is therefore possible that the composite Harris Hip Score might also be associated with EPLoS. Prospective research wherein data collection for the Harris Hip Score is standardised is required. Finally, we did not report the impact of EPLoS on healthcare expenditure or post-discharge complications. These outcomes can only be appropriately investigated through the conduct of prospective research studies.
In conclusion, we found several risk factors for EPLoS following primary hip arthroplasty in South African patients. These risk factors included sex, patient’s maximum walking distance, and extended duration of surgery. Further research is required to confirm our study findings, as well as address the limitations identified in our study.

**Ethics statement**

This study was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (Protocol: BE526/17). No benefits of any form have been received from a commercial party related directly or indirectly to the subject of this article.

**Declarations**

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

**Author contributions**

This study formed part of the postgraduate medical studies of NFD. NFD conceptualised the research idea, executed the research protocol, and wrote the manuscript. PV performed the statistical analysis, and provided a critical review of the manuscript. YM was involved in the conceptualisation of the research idea, performed the statistical analysis, and provided a critical review of the manuscript.

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Ryan PV  http://orcid.org/0000-0002-0957-6482  
Moodley Y  http://orcid.org/0000-0002-4119-1734

**References**

Pharmaceutical management of bone catabolism: the bisphosphonates

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Abstract

Background: Conditions associated with catabolism of bone are common and progress sub-clinically with devastating skeletal consequences. Over the past two decades, bisphosphonates have become increasingly popular for the preventative management of the skeleton in these conditions.

Methods: Recent literature pertaining to the mechanisms of action, clinical indications and complications of bisphosphonate therapy was retrieved using Google Scholar and Pubmed.

Aims of study: To provide an overview of the mechanisms of action, indications, contraindications and complications of the bisphosphonates available for clinical use in South Africa.

Results: Despite the availability of alternative management regimens, bisphosphonates remain the pharmaceuticals of choice for the management of hypercalcaemia and generalised catabolic skeletal disorders such as osteoporosis, skeletal metastatic disease, Paget’s disease of bone, glucocorticoid bone disease and osteogenesis imperfecta. Although adverse complications such as tachycardia, bowel and oesophageal irritation, pain, jawbone necrosis and atypical femur fractures are well documented, information remains limited on the long-term effects of bisphosphonate therapy on skeletal health. This manuscript provides an update on the mechanisms of action, principles applied to the selection of the most appropriate management regimen, monitoring of the response and complications of the bisphosphonates marketed in South Africa.

Level of evidence: Level 5

Key words: bisphosphonates, osteoporosis, bone metastases, Paget’s disease of bone, glucocorticoid bone disease, osteogenesis imperfecta, jaw bone necrosis
Introduction

Despite the development of innovative pharmaceuticals and auto-antibodies for the manipulation of skeletal metabolism (reviewed elsewhere), bisphosphonates (BPs) remain the first-line choice for the management of hypercalcaemia and several systemic catabolic skeletal disease states. BPs are derived from natural occurring pyrophosphates, which due to their calcium-binding properties, have been used for more than a century to soften water. Research performed by Procter and Gamble in the early 1960s on the prevention of dental caries and calculus deposits on teeth, exposed their affinity for bone and subsequent incorporation in the skeleton. It has subsequently been shown that approximately one-third of BPs absorbed are incorporated in the skeleton where they may persist lifelong. The remainder are cleared by the kidney without being further metabolised. During bone resorption, the incorporated BPs are released where they exert a profound local influence on the cellular components of the bone metabolic unit (BMU) and in particular the osteoclasts (readers are referred to elsewhere for more information on bone remodelling). These discoveries prompted pharmaceutical companies to manipulate the basic pyrophosphate structure of BP, and several patented drugs with different pharmacokinetics and clinical applications became available in a potentially lucrative market.

The purpose of this review is to highlight the mechanisms of action, clinical applications and complications of the BPs available in South Africa.

Mechanisms of action

First generation BPs

The early non-nitrogen-containing BPs, also referred to as the first generation BPs (Table I), promote osteoclast apoptosis through incorporation in adenosine triphosphate (ATP). The non-hydrolysable state of the modified ATP results in neutralisation of several enzymatic processes of the osteoclast which ultimately culminate in osteoclast apoptosis, thereby effectively reducing resorptive activity. The calcium-binding capacity of the first generation BPs, which retard mineralisation activity, is an outstanding characteristic which is enhanced by their resistance to neutralisation by alkaline phosphatase. This unique property is the reason for their specific clinical application.

Table I: Commercially available first generation BPs

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Route of administration</th>
<th>Potency</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate</td>
<td>Oral</td>
<td>10</td>
<td>Bonefos</td>
</tr>
<tr>
<td>Etidronate</td>
<td>Oral &amp; IV</td>
<td>1</td>
<td>Didroenel</td>
</tr>
<tr>
<td></td>
<td>(not listed in SA**)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tildronate</td>
<td>Oral</td>
<td>10</td>
<td>Skelid</td>
</tr>
<tr>
<td></td>
<td>(not listed in SA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Potency of osteoclast inhibition is relative to etidronate which is empirically set at 1 |
| Delivery molecule for (99m)Tc-based radiopharmaceuticals for skeletal imaging |

Clinical applications of first generation BPs

Due to the retardation of mineralising activity and binding of calcium, first generation BPs are not suited for the treatment of osteoporosis. Indications for their use are restricted to the management of hypercalcaemia which is commonly associated with disseminated skeletal malignancies and as an adjunct to the management of osteolysis resulting from bone metastases of malignant tumours.

During administration (either through the oral or intravenous route) the patient should be monitored for hypocalcaemia and secondary hyperparathyroidism as the drug tends to chelate blood calcium (the reason for its efficiency in correcting hypercalcaemia of malignancy). Furthermore, due to the chelating property, ingestion with milk or if the intravenous (IV) route is followed, with calcium-containing solutions like Ringer’s, is contraindicated. Similar to the second and third generation BPs, it should be used with caution in patients with impairment of renal functions, and regular renal function tests are advised before and during the course of therapy. Most of the other precautions and complications of BP therapy, which are discussed later, also apply to the first generation BPs. For more detail on the schedule of administration, drug interactions, complications and contraindications readers are referred to the manufacturers’ recommendations.

Second and third generation BPs

The second and third generation BPs, also known as the nitrogen-containing BPs, were developed by adding a nitrogen side chain to the pyrophosphate molecule. This addition increases the efficiency of osteoclast inhibition significantly. Various other modifications to the nitrogen-containing backbone contributed to the development of several commercially available BPs with differing potencies (Table II). Their method of action differs from first generation BPs. Nitrogen-containing BPs bind to a key enzyme in the pathway critical for cytoplasmic stress fibre assembly and membrane ruffling and, due to the subsequent osteoclast inhibition, apoptosis is induced. The effects are not restricted to osteoclasts only. Although their actions on other cells are less clear, they are known to exert a strong anti-apoptotic influence on the osteoblast lineage and therefore play a role in preserving the vitality of bone-forming cells. Unlike first generation BPs, these characteristics make second and third generation BPs most appropriate for the preservation of bone in catabolic skeletal disease.

Table II: Commercially available second- and third generation BPs

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Route of administration</th>
<th>Potency</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronic acid</td>
<td>Oral</td>
<td>500</td>
<td>Actonel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risedronate</td>
<td>Oral</td>
<td>2000</td>
<td>Actonel</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Oral &amp; IV</td>
<td>1000</td>
<td>Boniva</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>IV</td>
<td>10 000</td>
<td>Aredia</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>IV</td>
<td>100</td>
<td>Aredia</td>
</tr>
</tbody>
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| Potency of osteoclast inhibition is relative to etidronate which is empirically set at 1 |

Clinical applications of second and third generation BPs

Osteoporosis

Pharmaceutical intervention in osteoporosis must always be complemented by lifestyle and dietary measures which include weight-bearing exercise, cholecalciferol administration to patients...
Malignancies affecting the skeleton

The skeletal morbidity of myeloma is related to osteoclast-induced bone resorption with associated pain and hypercalcaemia. In a consensus statement of the Mayo Clinic Myeloma Group, IV pamidronate is recommended as the drug of choice for the management of these morbidities as pamidronate effectively suspends bone resorption, alleviates bone pain and corrects hypercalcaemia. Pamidronate is perceived to have a lower risk for inducing jaw osteonecrosis than the alternative, zoledronic acid. Upon remission, treatment is discontinued after two years. If remission is not achieved, pamidronate administration should be considered every three months at a reduced dosage.

In a recent update of 18 trials reporting on 4 843 men with advanced prostate cancer, BP therapy was shown to decrease the number of skeletal events and reduce disease progression. Although non-opioid and opioid analgesics are employed to manage metastatic bone pain, BPs can offer added pain reduction.

A joint review drafted by an expert panel of Cancer Care Ontario and the American Society of Clinical Oncology suggests that BP administration reduces bone recurrence and improves survival of postmenopausal patients with non-metastatic breast cancer. In separate studies, a substantial relief of the skeletal complications and pain have been demonstrated in patients with breast cancer receiving IV BPs. Of the oral BPs, only daily administration of ibandronate has been shown to be beneficial. The skeletal protecting action of BPs is advantageous particularly to women receiving oestrogen ablation therapy for hormone-sensitive breast cancer.

Other clinical applications

 Paget's disease of bone is characterised by an increase of bone resorption followed by defective bone formation. These processes result in a weak skeleton, deformities, skull enlargement and pain. BPs suppress bone resorption with subsequent normalisation of serum alkaline phosphatase concentrations and are therefore recommended for the management of the active and symptomatic phase of the condition. A recent practice guideline confirms that oral riseredronate, pamidronate and IV zoledronic acid are effective in this regard. BP therapy however does not eradicate the radiological changes, nor does it improve the deformities or reduce pain resulting from the associated osteoarthritis.

With present data available, BP therapy holds potential for the improvement of the quality of life of children with osteogenesis imperfecta. IV administration of pamidronate results in a significant increase in cortical bone thickness and trabecular bone volume. Success has also been reported with oral alendronate in the management of the consequences of this devastating genetic disease. Although the mechanism of action is not clear, it appears that the inhibition of osteoclast- induced resorption augments the defective process of bone formation. Although the use of BPs in children is cautioned against, the net clinical benefit of BP administration to children suffering osteogenesis imperfecta may outweigh its potential disadvantages.

Glucocorticoid therapy is the most important cause for pharmacologically induced osteoporosis. Glucocorticoids induce skeletal catabolism which is the result of induction of apoptosis of cells of the osteoblast lineage and activation of bone resorption through prolonging the lifespan of osteoclasts. Patients taking 2.5 mg or more prednisone per day for three months or longer and with a high risk for fractures can benefit from BP administration which should start at the onset of glucocorticoid therapy. Risedronate and alendronic acid are first choices and where these drugs are contraindicated, second line agents such as denosumab or teriparatide could be considered. Because of limited information on the advantages BP intervention in patients taking glucocorticoids, the American College of Rheumatology advises vitamin D and calcium supplementation without BP administration in patients with a low fracture risk.

Pamidronate and alendronic acid have been shown to reduce the markers of bone resorption during skeletal immobilisation.
and their protective influence on the skeleton, and reduction of hypercalcaemia and nephrolithiasis is promising. Management of the skeletal morbidity of paediatric conditions such as anorexia, juvenile rheumatoid arthritis and cystic fibrosis is awaiting data of long-term studies on whether the net benefit outweighs the potential complications. The embedding of modifications of BPs on implants creating bioactive surfaces which facilitate bio-integration and reduce implant failure will certainly gain momentum in the future.

**Adverse effects**

Despite considerable attention given to BP-related osteonecrosis of the jaw (ONJ), this complication is rare in patients receiving oral BPs: ONJ occurs in between 0.1% of myeloma patients and 5% of advanced prostate cancer patients on BPs. The majority of cases with ONJ were described in patients receiving high doses of IV BPs for myeloma and breast cancer (for a summary see Drake, et al.). The occurrence of ONJ is also related to the anti-angiogenic properties of the BP administered, host factors which include the presence of dormant jawbone infections and the efficiency of the immune response. A variety of infective agents are implicated, including Actinomycyes-like organisms and fungi. It is important to clear all foci of potential jaw bone sepsis before commencement of BP therapy and delay invasive dental surgery in patients receiving the medication. Patients with chronic ear infections may likewise develop osteonecrosis of the external auditory canal. Thigh, hip or groin pain should alert clinicians to another rare and not yet fully understood complication, namely atypical femur fracture.

An acute phase reaction is experienced by nearly a quarter of patients receiving the first IV dose of nitrogen-containing BP, and the incidence thereafter decreases progressively with each administration. This reaction is characterised by pyrexia with concomitant headache, arthralgia, myalgia and influenza-like symptoms, and pre-treatment with histamine receptor antagonists, antipyretics or corticosteroids may provide relief. An increase in serious atrial fibrillation (requiring hospitalisation) was reported in patients receiving IV zoledronic acid. Although verifiable data is not yet available for the other BPs, the risk appears to be smaller, if not negligible. This complication is an indication for considering an alternate management regimen. Conjunctivitis, uveitis, episcleritis and scleritis are rare complications of both oral and IV BPs. The incidence is less than 0.1%, appears to be limited to patients receiving risedronate, and resolves within weeks of discontinuation of therapy. Administration of BPs is contraindicated during pregnancy, lactation and in patients manifesting with allergic-type reactions against the drug.

**Conclusion**

The therapeutic roll-out of BPs for the management of generalised skeletal anabolism gained momentum over the past decade. Although the benefits of BP therapy outweigh the risks in several progressive skeletal anabolic states, the lack of long-term studies on large patient samples is hampering the generation of accurate data on the advantages and complication of BP therapy in some of the less common conditions. The long-term effects on the skeleton in particular will be interesting as the repair of micro-fractures, which contribute to skeletal strength, is impaired.

**Ethics statement**

The authors upheld the principles of non-maleficence and an accurate reflection of the literature during the preparation of the synopsis.

**Declaration**

The authors declare authorship of this article and that they have followed sound scientific research practice during the preparation thereof. This research is original and does not transgress plagiarism policies.

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**Author contributions**

All the authors were involved in the collection of relevant information from the literature. ReJ compiled the manuscript from the data received and all authors contributed to the revision of the manuscript and the final preparation of the submitted copy.

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**References**


The mainstay of osteoporosis medications is bisphosphonate treatment of which **alendronate** and **risedronate** are commonly prescribed in clinical practice. 

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**ACTAMAX 35 mg.** Each tablet contains risedronate sodium hemipentahydrate equivalent to 35 mg risedronate sodium. S3 A42/3.2/0455. NAM NS2 12/7.5/0035.

**Body mass index and Blount’s disease: a single academic hospital experience (Kgoedi MN, Rischbieter P, Goller R)**

1. Which of the following is a feature of Blount’s deformity?
   - a. External tibial rotation A
   - b. Genu valgus B
   - c. Genu recurvatum C
   - d. Genu procurvatum D
   - e. None of the above E

2. Which of the following is not a risk factor for the development of Blount’s disease?
   - a. African ethnicity A
   - b. Male sex B
   - c. Obesity C
   - d. Early walking age D
   - e. None of the above E

3. Which statement regarding Blount’s disease is true?
   - a. The mean BMI of patients with Blount’s disease is not statistically different from the BMI of the general population A
   - b. There is a relationship between early-onset Blount’s disease and bilateral involvement B
   - c. There is a relationship between BMI and the severity of Blount’s deformity C
   - d. Male patients with Blount’s disease have a higher BMI than their female counterparts D
   - e. None of the above E

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**Minimally invasive CT-guided excision of osteoid osteoma and other small benign bone tumours: a single centre case series in South Africa (Sluis Cremer T, Hosking K, Held M, Hilton TL)**

4. Regarding the natural history of osteoid osteoma, which statement is correct?
   - a. Malignant transformation is a rare complication. A
   - b. Progression to osteoblastoma is common. B
   - c. Osteoid osteoma is a transient condition that rapidly resolves. C
   - d. Spontaneous resolution does not occur. D
   - e. Spontaneous resolution occurs in all cases over a period of a number of years. E

5. Which type of chronic osteomyelitis was thought to be associated with reactivation of quiescent osteitis infection in adults?
   - a. Chronic post-operative osteomyelitis A
   - b. Chronic post-open fracture osteomyelitis B
   - c. Chronic contiguous osteomyelitis C
   - d. Chronic haematogenous osteomyelitis D
   - e. All of the above E

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**Reactivation of chronic haematogenous osteomyelitis in HIV-infected patients (Siyo Z, Marais LC)**

6. Which type of chronic osteomyelitis was thought to be associated with reactivation of quiescent osteitis infection in adults?
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   - d. Chronic haematogenous osteomyelitis D
   - e. All of the above E

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**Burden and profile of spinal pathology at a major tertiary hospital in the Western Cape, South Africa (Miseer S, Mann T, Davis JH, Marais LC)**

8. Which of the following treatment options for a small benign lesion of bone, such as an osteoid osteoma, has the highest risk of iatrogenic fracture?
   - a. Percutaneous intralesional curettage under image guidance A
   - b. Wide local resection through an open surgical approach B
   - c. Percutaneous image-guided radiofrequency ablation C
   - d. Open intralesional resection or the ‘burr-down’ technique D
   - e. Arthroscopic assisted resection of intra-articular lesions E

9. Regarding the management of osteoid osteoma, what is the most common indication for surgical management?
   - a. Failure of medical management to bring symptomatic relief A
   - b. Biopsy specimen for histological confirmation of diagnosis B
   - c. Prevention of malignant transformation occurring C
   - d. Prevention of growth disturbance in juxta-articular cases D
   - e. To address associated fractures E

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**Reactivation of chronic haematogenous osteomyelitis in HIV-infected patients (Siyo Z, Marais LC)**

10. The primary cause of spinal trauma noted in the study was:
    - a. Interpersonal violence A
    - b. Falls B
    - c. Motor vehicle accidents C
    - d. Pedestrian vehicle accidents D
    - e. Blunt trauma E
11. What percentage of spinal tuberculosis patients demonstrated an associated human immunodeficiency virus co-infection?

a. 12.6%  
b. 22%  
c. 10%  
d. 44%  
e. 16%

12. Which one of the following is not mentioned as an option for decreasing overall patient burden and resource use?

a. Improved surgical skills of district level surgeons to manage minor cases  
b. Dedicated anaesthetic teams for spinal surgery cases  
c. Stricter road traffic laws to reduce the incidence of motor vehicle accidents  
d. Use of district spinal units to manage spinal trauma and infection  
e. Employment of more spinal surgeons

13. Reducing post-operative length of stay:

a. Reduces hospital expenditure  
b. Increases hospital expenditure  
c. Reduces hospital resource utilisation  
d. Increases hospital resource utilisation  
e. Both (a) and (c)

14. The following are risk factors for extended post-operative length of stay following primary hip arthroplasty in South African patients:

a. Female sex, patient’s minimum walking distance, extended duration of surgery  
b. Diabetes, hypertension, female sex  
c. Extended duration of surgery, posterior surgical approach, general anaesthesia  
d. None of the above  
e. All of the above

15. With regard to differences in risk factors for extended post-operative length of stay between South African and overseas hip arthroplasty patient populations:

a. All the risk factors are the same between South African and overseas patient populations  
b. Only certain risk factors are shared between South African and overseas patient populations  
c. Differences in risk factors between South African and overseas settings necessitate setting-specific identification of risk factors  
d. Both (b) and (c)  
e. None of the above

16. The principal anti-resorptive action of bisphosphonates is related to:

a. Improvement of the blood flow in bone  
b. Increase of the mineral content of bone  
c. Suppression of osteoclast activity  
d. Facilitation of calcium uptake in the gastrointestinal tract  
e. Activation of vitamin D

17. Identify the false statement:

a. Care should be taken with the administration of bisphosphonates in renal patients  
b. Bisphosphonates may be associated with the induction of jawbone osteonecrosis  
c. Second and third generation bisphosphonates do not contain nitrogen  
d. Pyrophosphates are naturally occurring bisphosphonates  
e. Intravenous administration should be considered in patients with gastrooesophageal irritation

18. Bisphosphonates are incorporated in:

a. The hydroxyapatite in bone  
b. The collagen in bone  
c. Cells in the bone marrow  
d. The periosteum  
e. None of the above

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Mal-rotation of implants may lead to over 50% of painful TKA cases.\textsuperscript{5}

Anatomic shape of the Persona Tibia is designed to achieve proper rotation and optimal coverage, resulting in:

\textbf{Statistically significant decrease in anterior knee pain in vivo}\textsuperscript{7}

92% bone coverage\textsuperscript{6}

3% vs. 50% anatomic non-anatomic

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Mal-rotation of implants may lead to over 50% of painful TKA cases.\textsuperscript{5}
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