Avascular necrosis (AVN) of the hip in patients operated in the Orthopaedic Arthroplasty Unit at Chris Hani Baragwanath Academic Hospital

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

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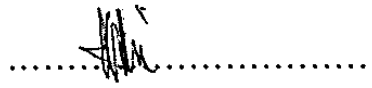
Declaration

I, Jephta Mwoyofiri declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Orthopaedic Surgery at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



(Signature of candidate)

25th day of July 2023 in Johannesburg

Dedication

In Dedication to my family

Ever supporting wife: Loice Masango Mwoyofiri

Sons: Akudzweishe and Tinaishe

Daughter: Mutsawashe

Presentations and publications arising from the research project

Nil

Abstract

Background: Avascular necrosis (AVN) of the femoral head is a progressive structural damage of the head of the femur because of interruption of blood supply to the subchondral bone resulting in the collapse of the head of the femur and secondary arthritis. Moreover, this chronic debilitating disease of the hip causes an immense contribution to the need for total hip arthroplasty (THA) and is common in young persons between the third and fifth decades of life. The aim of the study was to describe the causes of osteonecrosis of the femoral head (ONFH) in patients operated at Chris Hani Baragwanath Academic Hospital (CHBAH) Arthroplasty unit from 2017 to 2022.

Methods: A retrospective review of all patients operated between the above-mentioned period, was conducted through collecting the patients' demographic data, risk factors and treatment given.

Results: The study had 285 participants with AVN from a total of 838 patients who had hip surgery. There were 149 (52%) females and 136 (48%) males. The mean age was 51.7 years with a SD 11.4 years. Majority of the patients were in the age group: 50 – 59 years. The main risk factor of AVN was human immunodeficiency virus (HIV) with 117 (41%) patients. Those on highly active anti-retroviral therapy (HAART) were 115 (98%) patients. The median cluster of differentiation 4 (CD4) count was 584 (IQR 470 – 711) and the viral load was undetected in 29 of the 32 (91%) patients with recorded viral load results. Ficat/Arlet stage 4 had 199 (70%) patients and all our patients had total hip replacement.

Conclusion: ONFH contributes significantly to the burden of total joint arthroplasty in young patients. As our study has shown, there are several risk factors such as HIV, alcohol use and steroids being among the commonest. Our study draws attention to the significant burden that HIV has on hip pathology. HIV was the commonest cause of AVN at our local health institution and may be in the Sub-Saharan region. However, in our study we could not isolate HAART as a cause of AVN due to inadequate patient records. Majority of patients usually present with advanced stages of ONFH requiring a femoral head sacrificing operation due to late referral and long waiting list before surgery.

Acknowledgements

Special thanks go to the following colleagues:

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Table of contents

List of Figures

Chapter 1

Chapter 3

List of Tables

Chapter 1

Chapter 3

Nomenclature

ARV	Anti-retroviral drugs
ARCO	Association Research Circulation Osseous
ANFH	Avascular Necrosis of the Femoral head
AIDS	Acquired Immunodeficiency Syndrome
AVN	Avascular Necrosis
BMI	Body Mass Index
CD	Core Decompression
CD4	Cluster of Differentiation 4
CEO	Chief Executive Officer
CHBAH	Chris Hani Baragwanath Academic Hospital
COVID	Corona Virus Disease 2019
CVO	Curved Intertrochanteric Varus Osteotomy
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
HOD	Head of Department
M&E	Monitoring and Evaluation
MRI	Magnetic Resonance Imaging
ONFH	Osteonecrosis of the Femoral Head
PI	Principal Investigator

THA	Total Hip Arthroplasty
TJA	Total Joint Arthroplasty
UK	United Kingdom
USA	United States of America

CHAPTER 1

1. INTRODUCTION AND LITERATURE REVIEW

Avascular Necrosis (AVN) or Osteonecrosis of the Femoral Head (ONFH) is a progressive structural damage of the head of the femur because of interruption of blood supply to the subchondral bone resulting in the structural collapse of the head of the femur and secondary arthritis. Histology shows ischemia and marrow and osteocyte death (1). The condition is common in young persons between the third and fifth decades of life. In the United States of America (USA), ONFH affects 20,000 – 40,000 patients each year, and is estimated that more than a tenth of ONFH patients require total hip arthroplasty (THA) per annum (1). Bilateral hip joints are involved in up to 75% of patients (2). A review of the American National Inpatient Sample database in 2006 projected that primary THA procedures performed per year in patients younger than 55 years will increase to 28% by 2030 from about 21% (3). This proportion is however slightly lower outside the USA, such as in Canada, United Kingdom (UK) and Australia (3).

The aetiology, the way the disease develops, identification, and treatment of ONFH have been widely deliberated. It is believed to be the result of various conditions that interrupts vascularisation of the head of the femur (4). Cell death is believed to be from compromised microvascular capillary circulation from:

- Mechanical vascular interruption,
- Intravascular occlusion and
- Extravascular compression (4).

The commonest causes or risk factors of ONFH are trauma, corticosteroids use and alcohol use (4) while in South Africa the predominant indication for THA was found to be AVN in human immunodeficiency virus (HIV) seropositive individuals (5). Other rarer risk factors include blood dyscrasias such as sickle cell disease, polycythaemia vera, myeloproliferative neoplasm, and genetic hypercoagulable conditions, Gaucher's disease, Caisson's disease, smoking, radiation, and malignant processes among others (4). HIV has been associated with ONFH. The pathomechanism is postulated that ONFH in HIV may be a combination of the disease process itself, with anti-retrovirals (ARVs) that predispose to vasculitis, or a combination of predisposing factors (4). Trauma causes ONFH by disrupting the retinacular branches mainly

from the medial circumflex femoral artery. The traumatic events include dislocation or fractures around the hip (6).

Corticosteroids are cited as the main cause of non-traumatic AVN of the head of femur, contributing to its development in 25 – 50% of patients (7). Corticosteroids are used as a first-line anti-inflammatory in many medical conditions such as systemic lupus erythematosus, bone marrow transplantation and various blood malignancies (8). In patients with systemic lupus erythematosus using glucocorticoids, AVN of the head of femur was found in 15 – 35% (7). The actual pathophysiology of glucocorticoids leading to ONFH is still unknown (4). Corticosteroids have been associated with abnormal fat metabolism resulting in accumulation of lipids in marrow causing mechanical blockage, raised extravascular intraosseous pressure and diminished venous and arterial blood circulation to the femoral head (9).

Although corticosteroids are commonly used and have been studied widely, it has been difficult to find the risk amount or duration of corticosteroids that lead to AVN and is probably multifactorial including genetic predisposition, corticosteroid exposure, and the medical condition being treated (7). In trying to come up with a consensus on the dose and duration of glucocorticoid use that is a diagnostic cause of ONFH, the Association Research Circulation Osseus (ARCO) group came up with criteria that they only recommended for use to homogenise clinical research but not as a diagnostic criterion.

Too much alcohol use is another common cause of non-traumatic ONFH, reported in 20% to 45% of ONFH patients (10). Suggested pathogenesis of alcohol induced ONFH includes abnormal fat accumulation causing decreased capillary blood supply to the head of the femur and leading to diminished bone marrow formation and osteogenesis (11). Byung-Ho Yoon, et al. found in a meta-analysis among Japanese individuals, a relationship of alcohol intake and AVN of the head of femur. Former alcohol intake has a marginally increased risk of ONFH while current alcohol intake has significant increased risk of ONFH. The dose-response meta-analysis showed that the risk of the disease rose by 35.3% for every 100 g/week and by 44.1% for every 500 g drink-years. The increased risk of ONFH with current intake and the amount of is a non-linear relationship that show idiosyncratic patterns (11). This study unfortunately included only people of Japanese origin, thus cannot be taken as representative of alcohol intake response to all individuals due to different genetic predispositions.

The ARCO group has tried to come up with a cut off amount of alcohol intake that will result in ONFH in 2015. The group came up with the following criteria:

- Intake of alcohol > 400 mL/week of pure ethanol for greater than six months;
- diagnosis of ONFH within one year of such an amount of alcohol intake; and
- no other risk factor(s) of OFNH in the same patient. This however has only helped in standardising clinical studies concerning alcohol associated ONFH but not for diagnostic purposes (10).

Diagnosis of ONFH is made upon taking history, examination, and investigations. History elicits hip or groin, back or knee pain and a thorough search of risk factors such as mentioned above. Examination findings include groin tenderness, limited range of motion especially restricted internal rotation of the hip and antalgic or Trendelenburg gait (12). Imaging is the mainstay of diagnosis of ONFH. Plain radiographs are the first step. Very early stage of the disease is not detectable on plain radiographs. Orthopaedic surgeons, therefore, must suspect ONFH in younger patient presenting with hip pain with normal X-rays. In later stages on anteroposterior (AP) pelvis and lateral views, femoral head changes that are seen include sclerosis, cysts formation and crescent sign. A crescent sign is an area of lucency in the head of the femur's subchondral bone, which is a fracture because of bone death and ensuing repair attempts. In advanced stages of ONFH the femoral head flattens or collapses, and secondary arthritic changes are noted. Plain radiographs are important for follow up of progression as well as classification of ONFH (13).

Magnetic Resonance Imaging (MRI) is the method of choice for patients with suggestive clinical findings where normal radiographs for accurate diagnosis and staging of the disease are not sensitive. In addition, MRI can be used to assess the extent and prognosis of the disease as well as guide the follow up after surgical treatment. On the accuracy of diagnosis, Ya-Zhou Zhang et al. found that the sensitivity and specificity of MRI were 93% and 91%, respectively (14). On Tl-weighted sequences, a subchondral "bandlike" lesion is pathognomonic while on T2-weighted views the "double-line" sign is virtually diagnostic of AVN. In later stages of AVN a crescent sign, collapse and hip osteoarthritis are easy to see on MRI. Computed tomography (CT) scan can show osteosclerosis around the dead bone, recovered bone as well as subchondral bone fracture but is rarely used for diagnosis of AVN due to considerable

radiation exposure (15). Other investigation modalities that can be employed are radio scintigraphy, biopsy, and histology as well as Digital subtraction angiography (15).

Several classifications for ONFH were developed. Ficat and Arlet, Japanese Orthopaedic Association, University of Pennsylvania/Steinberg, and the ARCO are the four most quoted (4). The Ficat and Arlet classification system evolved prior to the presence of MRI, and it uses bone scan, clinical symptoms, and X-ray findings (13). Although it is the most used classification system, it does have some limitations including that it excludes the size or area of the necrotic bone lesion, which is vital in treatment and prognosis, and there is poor interobserver and intraobserver reliabilities (13). An example of Modified Ficat and Arlet classification is shown in Table1.1 below (12):

Table 1.1: Modified Ficat and Arlet classification system (introduced in 1985) (12).

Stage	**Findings**
0	Normal X-rays (Hip is silent)
I	Small degree of abnormality with patchy/opaque areas, mild osteopenia
II	Cystic lesions or Sclerosis IIa: Absent crescent sign IIb: Crescent sign but no flattening of the head of femur
III	Flattening or collapse the head of femur.
IV	Collapse of head of femur and degenerative changes of the hip

In 1991, the ARCO committee developed the ARCO staging system by combining the Ficat, the Japanese Investigation Committee and Steinberg staging systems on ONFH. An updated system was developed in 2019. It has five stages as shown in Figure 1.1 below (15).

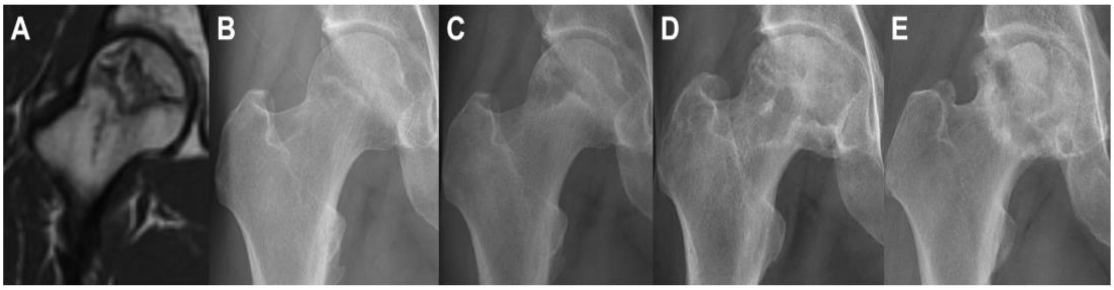


Figure 1.1: ARCO staging. (**A**) T1-weighted coronal MRI image. (**B**) Stage 11: Focal osteoporosis and osteosclerosis in the femoral head. (**C**) Stage 111A: subchondral collapse less than 2mm and marginal sclerosis along the lesion are seen. (**D**) Stage 111B: marked collapse of the femoral head more than 2 mm is noted. (**E**) Stage IV: fragmentation of the necrotic lesion and progress of the joint space narrowing with acetabular change are seen (15).

Classification of ONFH is useful in predicting treatment outcomes and prognosis (16). Prevention of ONFH may be possible if risk factors such as alcohol use among others are identified and are eliminated or avoided (16). In situations where steroids are essential for the treatment of the primary disease, it may be difficult to avoid their use.

Non-surgical treatment includes restricted non-weight bearing and physical therapy in the early stages of ONFH. However, they have been of limited efficacy in preventing progression of ONFH. Medications that have been used alone or in combination with other modalities include anticoagulants, fibrinolytics, vasodilators, lipid-lowering agents and bisphosphonates (17). Peipei Guo et al. showed that anticoagulants may be of benefit in Ficat stages 1 and 2 but there is still need for randomised control studies at a larger scale to confirm their findings (18). Surgical treatment is divided into femoral head preserving procedures and hip joint replacement. Femoral head preserving procedures include core decompression, osteotomy, and vascularised and non-vascularised bone grafting for early stages of ONFH (Ficat 0 – 2) (12).

Core decompression (CD) lowers intraosseous pressure and may improve blood circulation to the femoral head, thus potentially delaying or preventing femoral head collapse. It can be done using a single drilling with a trephine of 8 – 10 mm core diameter or by multiple drilling with

wires of 3 – 4 mm diameters. This method can be combined with biologically active adjuvant substances. According to research by Kun-chi Hua et al., the success rates of CD+ Marrow (74.0%) and CD+ Autologous Bone (A.B) (81.0%) are both greater than the success rate of CD alone (65.0%) (19). Bone grafting has been used in pre-collapse ONFH either as vascularised or non-vascularised bone graft. Non-vascularised bone grafts provide structural support and a scaffold for new bone creep while vascularised grafts have the added advantage of providing a revived blood supply. This technique has been recommended in young patients with pre-collapse stages of ONFH (4).

Osteotomies are done to rotate the diseased segment of the hip away from the weight-bearing area and replace it with a normal viable bone (17). In younger patients (< 50 years), Yusuke Osawa et al. found the clinical results of Curved Intertrochanteric Varus Osteotomy (CVO) and THA for ONFH were almost equivalent (20). However, THA after CVO is technically difficult due to anatomic deformity. THA is the option of choice in cases of advanced secondary arthritis and in failed joint-preserving surgical treatments with excellent results in pain relief and survivorship (20). THA for ONFH done in younger individuals used to be associated with implant loosening and need for revisions but due to the newer implant generations comparable results to that of primary total hip arthroplasty done for primary osteoarthritis have been achieved (20). Poor bone stock due to the AVN and medications being used is commonly found in patients with ONFH and care during THA must be taken. Xin Yu Mei et al. found in their systemic review study good outcomes with THA in younger patients with five- and 10-year revision-free implant survival of 98.7% and 94.6%, respectively; and progressive radiolucency was not commonly reported (27). To the best of our knowledge, there has not been a local study that was done on the incidence, risk factors and treatment of AVN of the femoral head at Chris Hani Baragwanath Academic Hospital (CHBAH) and that has prompted us to do this retrospective research at this health institution.

CHAPTER 2

2. METHODOLOGY

2.1 Study Aim: To describe the causes of AVN of the hip in patients operated in the Orthopaedic Arthroplasty Unit at CHBAH.

2.2 Study Objectives:

- To document the patient demographics: Age, gender, and body mass index (BMI)
- To establish the prevalence of AVN (*n*)
- To establish the risk factors for AVN
- To analyse the treatment prescribed (conservative, surgical)

2.3 Research Design

The site of study was CHBAH. It was a retrospective study from 01 January 2017 to 30 November 2022.

2.4 Data collection

The principal investigator (PI) (Dr Mwoyofiri) obtained records of all patients who were operated under the Orthopaedic Arthroplasty Unit during the stated period. All patients who had hip operations had their X-rays analysed to determine their diagnoses and classifications. Moreover, X-rays were reviewed by a senior Orthopaedic surgeon (Prof Frey) in order to eliminate errors in diagnosing and classifying the patients' hip pathology. Records of patients with AVN of the hip had their history, examination, investigations, and treatment further analysed. The patients' demographics namely the gender, age, and BMI as well as the risk factors for AVN of the hip were recorded. The patients' HIV status, CD4 count, viral load, and ARV protocol were noted, as well as their HIV status. According to Ficat and Arlet classification, AVN was given a score. The PI then evaluated the patient's sort of procedure.

2.5 Patient Selection Criteria

Inclusion criteria:

- Patients operated in the Orthopaedic Arthroplasty Unit at CHBAH.
- Patients older than 18 years.

Exclusion criterion:

- Patients with incomplete records.

2.6 Data Analysis

The sample size at power 80% and 95% confidence interval is 139 patients (**minimum sample size**) considering 10% have AVN caused by corticosteroids therapy (Moya-Angeler *et al.* 2015) (12) as shown by Table below:

Sample Size for Frequency in a Population	
Population size (for finite population correction factor or fpc) (*N*):	1000000
Hypothesized % frequency of outcome factor in the population (*p*):	10%+/-5
Z = Normal standard deviation at 80%=1.96	
Confidence limits as % of 100(absolute +/- %) (*d*):	5%
Design effect (for cluster surveys-*DEFF*):	1
Sample Size(*n*) for Various Confidence Levels	
Confidence Level (%)	**Sample Size**
95%	139
80%	60
90%	98
97%	170
99%	239
99.9%	390
99.99%	545
Equation	
Sample size $\boldsymbol{n = [DEFF*Np(1-p)]/ [(d^2/Z^2_{1-\alpha/2}*(N-1) +p*(1-p)]}$	

The information was collected on a data collection sheet that had different variables (patient's demographics, risk factors, treatment done etc). All the data were captured on Excel and imported to STATA for analysis. A de-identified excel spreadsheet was imported, using STATA software version 15, different commands assisted in cleaning the data. Data cleaning processes included checking for duplicates, missing values, recoding and categorising variables. This was a quality assurance process.

Descriptive statistics was conducted. Categorical variables were presented as frequency and percentages. The continuous variables such as the age was presented as mean ± standard deviation or median and interquartile range (if not normally distributed). Missing information was checked on each variable. Association of categorical variables such as the risk factors and gender were assessed using the Pearson's Chi-Square or Fisher exact test. Graphs were also generated**.** All statistical tests analysis were two sided and *p*-values < 0.05 were statistically significant.

2.7 Limitations

Only one risk factor for AVN of the hip was recorded per patient and this could affect the outcomes of the risk factor profile of the population under investigation. Several patients did not have their CD4 count, and viral load recorded as well.

CHAPTER 3

3. RESULTS

Table 3.1 shows that the study had 285 participants with AVN from a total of 838 participants who had hip surgery. Females were 149 (52%) and males were 136 (48%). The mean age was 51.7 (SD 11.4) years. Majority of participants were age group 50 – 59 years. The main risk factor of AVN was HIV with 117 (41%). Those on highly active antiretroviral therapy (HAART) were 115 (98%) patients. The median CD4 count was 584 (IQR 470 – 711). The viral load was undetected in 29 of the 32 (91%) patients who had recorded viral load. There were 100 (35%) overweight patients, and 96 (34%) patients were in the three classes of obese. Ficat/Arlet stage 4 had 199 (70%) patients. All patients had total hip replacement done.

Table 3.1: Summary of results of data collected.

Variable(N)	N(%)/ Mean(SD)/Median(IQR)
Prevalence of AVN in THA (*n*) 285/838	285(34)
Gender (285)	
Female	149(52)
Male	136(48)
Age	51.7(11.4)
20 - 39	42(15)
40 - 49	71(25)
50 - 59	102(36)
60 - 69	56(19)
70+	14(5)
Risk factors for AVN (285)	
Alcohol	59(20)
Unknown	54(18)
HIV	117(41)
Lupus	8(3)
Steroids	25(8)
Other (Caisson, Perthes, Radiation, TB)	5(1)
Trauma	17(6)
HAART (117)	
Yes	115(98)
Unknown	2(2)
CD4(57)	581(470-711)
Viral load (32)	
Not detectable	29(91)
>400	3(9)
BMI category (283)	28(5.4)
Underweight	6(2)

Normal **Overweight** **Obese C1** **Obese C2** **Obese C3**	81(29) 100(35) 66(23) 18(7) 12(4)
Ficat/Arlet (285) **2B** **3** **4**	 10(3) 76(27) 199(70)
Treatment prescribed (285) **THR**	 285(100)

3.1 Age and Gender

Figure 3.1 shows that the majority of female patients were in the age group 40 – 49 years making 29% while majority of males were in age group 50 – 59 years making 44%. In both gender, the overall age group range with majority was 40 – 59 years making up 61% of the total number.

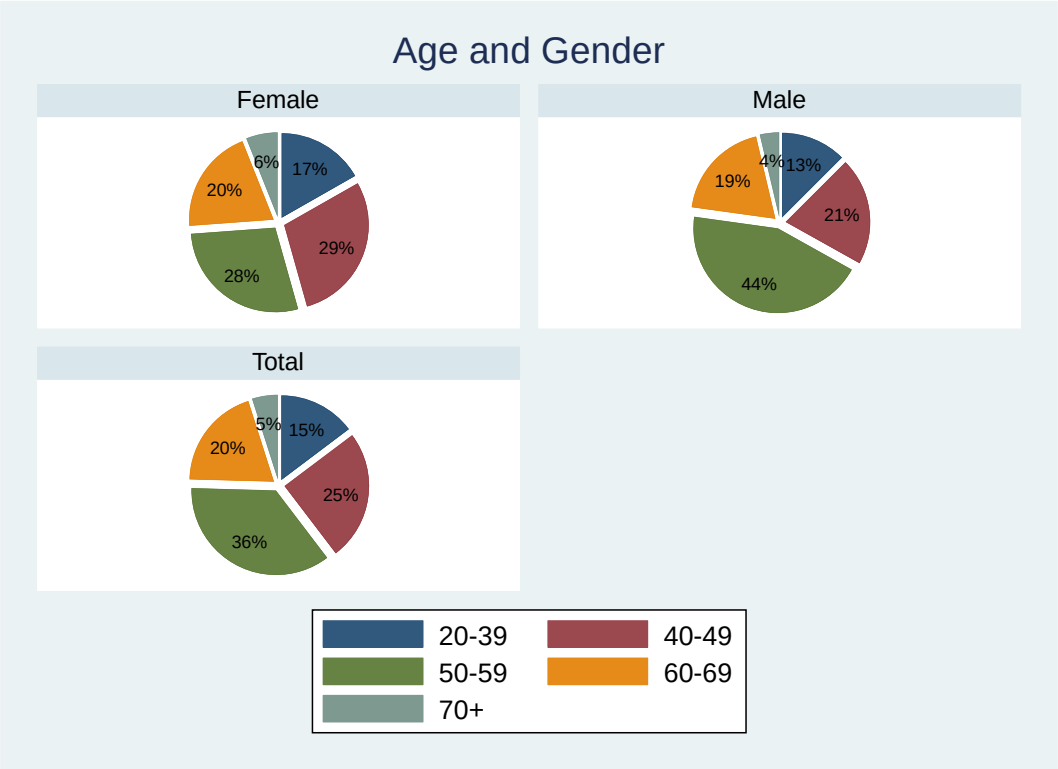


Figure 3.1: Age and gender distribution.

3.2 Risk Factors

Table 3.2 shows the different risk factors in relation to patient variables. HIV was the highest risk factor 40 – 49 year age group while Alcohol and trauma contributed the most in the 50 – 59 year category. Alcohol was the most contributing risk factor in males while majority of females had HIV. Overweight category was the most frequent in all risk factors. Ficat/Arlet stage 4 had highest frequencies except in Lupus where stage 3 was higher than stage 4 (50%).

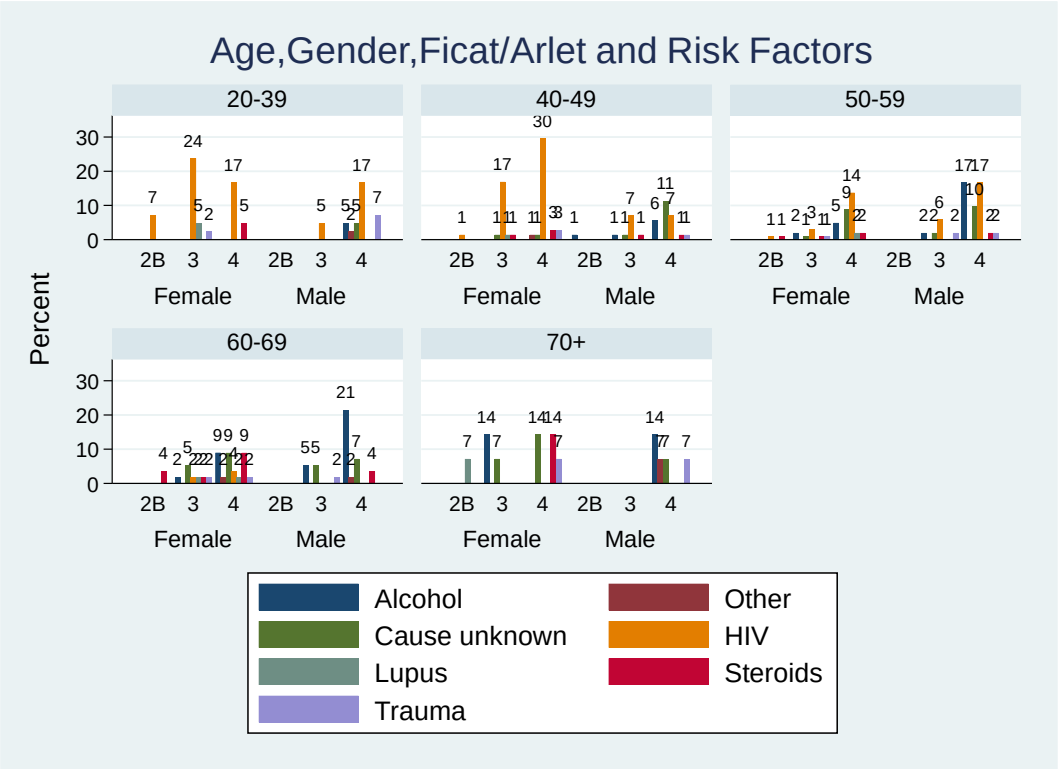
Table 3.2: Distribution of risk factors in different patient factors.

Variable (N)	Alcohol	Other	Unknown	HIV	Lupus	Steroids	Trauma	*p*-value
Age category								<0.001
20 - 39	2(3)	1(20)	2(4)	29(25)	2(25)	2(8)	4(24)	
40 - 49	6(10)	1(20)	11(20)	44(38)	1(12.5)	5(20)	3(18)	
50 - 59	26(44)	0	22(41)	41(35)	2(25)	6(24)	5(29)	
60 - 69	21(36)	2(40)	15(28)	3(3)	2(25)	10(40)	3(18)	
70+	4(7)	1(20)	4(7)	0	1(12.5)	2(8)	2(11)	
Gender (285)								<0.001
Female	15(25)	2(40)	23(43)	75(64)	8(100)	19(76)	7(41)	
Male	44(75)	3(60)	31(57)	42(36)	0	6(24)	10(59)	
BMI category								0.341
Underweight	2(3)	0	0	3(3)	0	1(4)	0	
Normal	22(38)	0	14(26)	32(28)	0	7(28)	6(35)	
Overweight	21(36)	2(40)	19(35)	40(34)	4(50)	7(28)	7(41)	
Obese C1	9(16)	3(60)	14(26)	30(26)	2(25)	7(28)	1(6)	
Obese C2	3(5)	0	2(4)	7(6)	2(25)	1(4)	3(18)	
Obese C3	1(2)	0	5(9)	4(3)	0	2(8)	0	
Ficat/Arlet (285)								0.029
2B	1(2)	0	0	5(4)	1(13)	3(12)	0	
3	11(18)	0	12(22)	39(33)	4(50)	4(16)	6(35)	
4	47(80)	5(100)	42(78)	73(62)	3(37)	18(72)	11(65)	
Treatment prescribed (285)								0.589
THR	59(100)	54(100)	117(100)	8(100)	25(100)	17(100)	5(100)	

3.2.1 Human Immunodeficiency Virus (HIV)

One hundred and seventeen (41%) patients were HIV positive. One hundred and fifteen of them were on HAART. Only 57 patients had their CD4 counts recorded while viral load was recorded in only 32 patients. Of those who had recorded viral load, 29 of them had undetectable levels (<50 copies/ml). All recorded CD4 count were between 400 and 711 with a mean value of 581.

Figure 3.2 shows that the trend of HIV as a risk factor is high in the age groups 20 – 59 years and mostly among females with Ficat/Arlet stage 3. Alcohol risk factor is mostly in males in the age group 50 – 70+ years with Ficat/Arlet stage 4 and in females, it is in 70+ age group with Ficat/Arlet stage 3. Steroids are a risk factor in females 70+ age with Ficat/Arlet stage 4.



*Other risk factors included Caisson, TB, Perthes and Radiation

Figure 3.2: Age, Gender, Ficat/Arlet and Risk Factors.

3.2.2 Age and BMI

Figure 3.3 shows that the highest mean age was for alcohol risk factor 57.6 (SD 9) years and lowest mean age was HIV risk factor 45.8 (SD 8) years. The highest mean BMI was for Lupus risk factor 30.6 (SD 5) years and lowest BMI was alcohol risk factor 26.6 (SD 5) years.

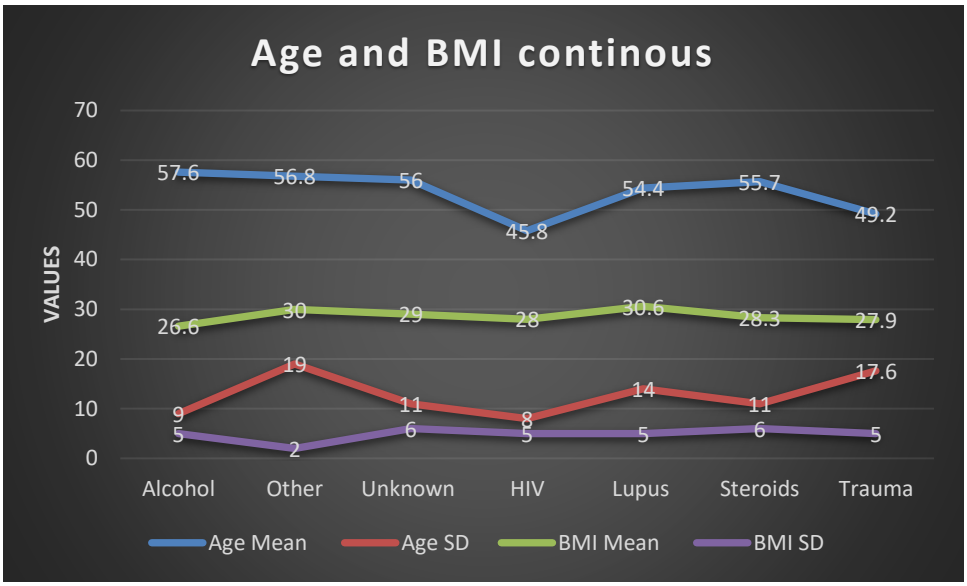


Figure 3.3: Age, BMI, and Risk Factors.

CHAPTER 4

4. DISCUSSION

4.1 Prevalence

Avascular necrosis of the head of femur was found to be the primary diagnosis in 34% of THA cases done in the CHBAH Arthroplasty Unit between 01 January 2017 and 30 November 2022 (see Table 3.1). This shows a high prevalence of AVN of the hip compared to other regions of the world. In the USA, it accounts for approximately 10% of THA done annually while in the United Kingdom, ONFH is the third most prevalent cause for THR in patients below the age of 50 years (22). The reasons for the difference between our study and the other countries may be due to the difference in the risk factors prevalent in different countries, as we will discuss below. It also appears that different registries report varying prevalence of AVN of the femoral head. The Canadian, Swedish, and Australian registries have shown that ONFH accounts for about 2.8% to 6% of all primary total hip replacements (6). Our study was conducted at an institution that is in an urban area and that might be a contributing factor to the differences in AVN prevalence. In China, a large-scale epidemiological survey of non-traumatic AVN showed a higher prevalence in northern residents (0.85%) compared to southern residents (0.61%) and lower in rural residents than in urban residents (16).

The prevalence of osteonecrosis of the femoral head (ONFH) is rising (23). We could, however, not show the yearly incidence rates of AVN over the period of our study because there was a deliberate postponement of some elective arthroplasty cases in 2020 and 2021 as only emergency operations were being done during the height of the Corona virus disease 2019 (Covid-19) pandemic. However, cases of AVN are expected to increase in the next few years due to the extensive use of Corticosteroids in the treatment of Covid-19 (24).

Many studies have shown that AVN of the head of femur affects young people aged between 20 and 55 years (22,23,27) with an average age of 47 years (6). Our study found almost similar results with the most affected age range being between 40 and 59 years, which contributed to 61% of the patients with an average age of 51.7 years (see Table 3.2).

Whilst we found a slightly higher number of patients, being females (52%) compared to males (48%) (see Table 3.1), Daniel Petek, *et al*. reported a male to female ratio of 3:1 (6). The

difference might be due to the difference in the prevailing risk factors as we found in our research compared to other regions of the world. We found more females, 64% *versus* 36% of males being HIV positive (see Table 3.2) while according to Lin *et al*. (2013), individuals with HIV were more likely to be male, younger, and to have a history of femoral head AVN. (5).

4.2 HIV

In our study (see Table 3.1), we found HIV was the commonest risk factor for developing AVN of the femoral head. It was found in 41% of the patients operated with ONFH at our institution. It was followed by alcohol (20%), steroids (8%), trauma (6%), Lupus (3%) and other rarer causes contributing 1% of the cases. In about 18% of patients, we could not find a risk factor and we contribute these to diseases that we do not test for routinely. These findings are different from many other studies that report excessive alcohol use and steroids being the commonest causes accounting to more than 80% of cases (23) especially in developed countries. The difference may just be due to the differences in HIV positive prevalence in different parts of the world. Globally there are 36.9 million people living with HIV with South Africa having the highest number (7.2 million) as a country in the world (5). In Sub Saharan Africa, the adult prevalence of HIV in 2013 was approximately 4.7%, compared with 0.3% in Europe and North America. Within Sub Saharan Africa, prevalence estimates also vary between countries; for example, in 2013 the estimates for Malawi and Botswana were 21.9% and 10.3%, respectively (28). HIV has been shown to be associated with Osteonecrosis in many studies (5,8,26,29). The high prevalence of HIV as a risk factor of AVN in our institution may explain the high prevalence of AVN (34%) in patients who had THA in our period of study. Our study finding of HIV prevalence in Osteonecrosis is consistent with the findings in other studies done in the Sub Saharan Africa as reported by Lubega *et al*. who found 44% of patients with avascular necrosis had HIV (28).

Almost all the patients with HIV and ONFH were below the age 60 years (97%) with the most affected age range being 40 – 49 years (38%) (see Table 3.2) and having the lowest mean age (45.8 years) compared to all other risk factors (see Figure 3.3). This shows a preponderance for HIV causing ONFH in a younger age group compared to other risk factors such as alcohol use where 80% was seen in the 50 – 69 year age group as well as Steroids use where 64% was seen in the 50 – 69 year age group. The highest HIV seroprevalence in South Africa is among individuals aged 15 – 49 years (5) and this might explain the young age group affected by AVN

due to HIV. Of the HIV positive patients with AVN, 98% were on HAART while the remainder had no records of whether they are on the medication or not (see Table 3.1). HIV and HAART are independent risk factors for osteonecrosis of the femoral head (5,8,29).

The percentage of patients on HAART is higher than that found in a study of HIV seroprevalence in arthroplasty done in an institution located in the same city as ours where they discovered that 86.1% of patients were taking HAART already (5). The high number of patients on HAART might be a result of the deliberate efforts by country's Health Department to ensure at least 90% of HIV positive patients be on HAART. However, in our study population the ARV regimens that the patients were on were not recorded, hence, we could not further discuss the association between AVN and the type of ARVs the patient is taking as other studies have shown (26). There was also poor recording of the patients' immunological status markers, CD4 count or viral load with only 32 patients having their viral loads recorded (see Table 3.1). However, 91% of the viral loads were at undetectable levels showing a good suppression of the virus. This resonates well with CHBAH arthroplasty policy of optimising all elective patients with comorbidities including HIV before their operations done.

4.3 Alcohol

Alcohol accounted for the second commonest (20%) risk factor of AVN after HIV in our study population (see Table 3.1). This is consistent with other studies findings that 20 – 30% of hip osteonecrosis is due to overuse of alcohol (21,22,23). However, similarly to other studies, we could not get further information about alcohol intake to quantify their drinking habits. The estimates of alcohol consumption could be biased due to limited human memory, a large time variation in drinking, diverse ethanol content, and various categories of drink (10).

Three quarters of our patients with alcohol associated ONFH were males (see Table 3.2). This may be pointing to more males taking excessive amounts of alcohol compared to females. We could not find a study that show gender distribution in ONFH due to excessive alcohol use. In addition, alcohol was associated with the lowest mean BMI (26.6) among all other risk factors (see Figure 3.3). Majority of the patients affected by AVN with alcohol use were in the age group 50 – 59 years (44%) which coincided with the age group of most males (44%) (see Figure 3.1). This might suggest an association between the age group of patients affected by AVN due alcohol use and male sex.

4.4 Lupus and Steroids

Eight per cent of osteonecrosis was due to steroids use in our study (see Table 3.1). This is way below the findings in other studies in other parts of the world with estimates of 25 – 50% of patients due to use of steroids and accounting for the commonest cause of ONFH (7,21,22). This might point to poor awareness of the risk of developing AVN with corticosteroids use in some clinicians who prescribe them for other medical conditions such as rheumatoid arthritis, respiratory diseases, and organ transplant patients. Mont *et al*. (2020) recommends high levels of suspicion in at-risk patients to diagnose ONFH early (23). Genetic polymorphisms might explain differences in vulnerability to individuals to AVN using corticosteroids as was reported in Konarski *et al*. (2022) article. Systemic lupus erythematosus (SLE) accounted for 3% of AVN cases in our study (see Table 3.1). This is almost in agreement with other reports that found Lupus in 3 – 30% of cases (21).

We could not separate patients on steroids with SLE and those who are not taking steroids due to unavailability of the information in the records. Reports show that in patients with SLE treated with corticosteroids, a higher chance of AVN was observed (22). SLE and use of corticosteroids as independent risk factors were each found almost evenly distributed in all age groups in our study (see Table 3.2). This suggests that SLE and use of corticosteroids independently affect patients in all age groups.

4.5 Trauma

ONFH due to trauma was found in 6% of cases (see Table 3.1) and of these 59% were males in our study (see Table 3.2). Trauma was the cause of AVN in all age groups with no statistical difference in the percentage contribution due to the small sample size (17 patients) of trauma patients. In other reports, trauma is one of the most common causes of osteonecrosis with incidences after neck of femur fracture varying from 11 to 86% (8).

4.6 Other risk factors

At our institution, other causes of ONFH that were identified included Caisson's disease (one case), radiation (one case), Perthes disease (two cases) and childhood history of TB of the hip (one case) (see Table 3.1). These are rare causes of ONFH reported in literature (21,22) similar to our population. The one case of Caisson's disease was a patient who was a former deep-sea diver in the South African National Defence Force's aqua unit.

4.7 Ficat/Arlet

We used the Ficat/Arlet classification of ONFH in our study because it is the most frequently used system in the world (63%) (8). Moreover, the Ficat/Arlet classification is a classification, we are most familiar with. Patients operated at our institution had either Ficat/Arlet stage 3 or 4 in 97% of the cases while stage 2B account for the rest (see Table 3.2). This shows a tendency to late presentation and diagnosis of patients with AVN as we know that if AVN is left untreated it progresses to secondary osteoarthritis (Ficat/Arlet stage 4) of the hip in 70 – 80% of cases (22). We could only identify advanced stages of AVN (see Figure 3.2) as we depend on traditional radiography to make a diagnosis and classify ONFH at our institution. Early stages of AVN would require MRI scan to identify (22) but it is expensive and not widely available. As shown in Figure 3.2, most females presented in Ficat/Arlet stage 2B and 3 of AVN while most men presented in Ficat/Arlet stage 4 in almost all age groups. This difference may be because females seek medical treatment earlier than males.

4.8 Treatment

It was not surprising that all our patients received a head sacrificing procedure (THA) due to the advanced nature of their AVN stages. Total hip arthroplasty (THA) is the preferred treatment in patients with severe pain, loss of hip function, and a significant femoral head collapse (22). THA offers patients with AVN excellent outcomes similar to those in patients with a diagnosis of primary osteoarthritis (22). Hip resurfacing is a more bone preserving form of total hip arthroplasty. It is rarely done at our institution for ONFH due to the magnitude of femoral head destruction, with only one case done in our study. It is however, an effective treatment modality in strictly selected patients (25), as aseptic loosening complicates femoral prosthesis in ONFH (23).

4.9 Recommendations

Based on the results from this study the following recommendations are made:

- Clinicians should exercise a high level of suspicion in at-risk patients (those who have HIV, consume excessive alcohol, use corticosteroids, etc.) to diagnose early stages of ONFH.
- There must be collaboration between Orthopaedic surgeons and Rheumatologists and HIV specialists for early detection and referral of patients with ONFH.

- HIV must be ruled out in individuals who have ONFH.

CHAPTER 5

CONCLUSION

Avascular necrosis of the femoral head is a common hip pathology at our local health institution affecting mainly young patients. It contributes significantly to the burden of total joint arthroplasty. As our study has shown, there are several risk factors with HIV, alcohol use and steroids among the most common. Our study draws attention to the significant burden that HIV has on hip pathology. HIV is the commonest cause AVN at our local health institution and may be so in the Sub-Saharan region. Most patients that present with advanced stages of ONFH will require total hip arthroplasty.

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Appendices

Appendix A: Data collection sheets

Appendix B: Ethics clearance certificate

Appendix C: CEO permission letter

Appendix A: Data collection sheet

Study Number	**Age**	**Gender**	**BMI**	**HIV status (Positive Or Negative)**	**ARV Regimen**	**Alcohol Intake (Yes or No)**	**Trauma**	**Steroid use (Yes or No)**	**Other Risk Factors**	**Ficat stage**	**Treatment (Surgical or conservative)**

Appendix B: Ethics Clearance

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr J Mwoyofiri

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220428

NAME: (Principal Investigator)	Dr J Mwoyofiri
DEPARTMENT:	School of Clinical Medicine Department of Surgery Division of Orthopaedic Surgery Medical School University
PROJECT TITLE:	*Avascular necrosis (AVN) of the hip in patients operated in in the Orthopaedic Arthroplasty Unit at Chris Hani Baragwanath Academic Hospital* Change of study title noted in 2023/01/09
DATE CONSIDERED:	2022/04/29
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor S Magobotha and Dr M Lingo
APPROVED BY:	Dr N Naran, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/07/15

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

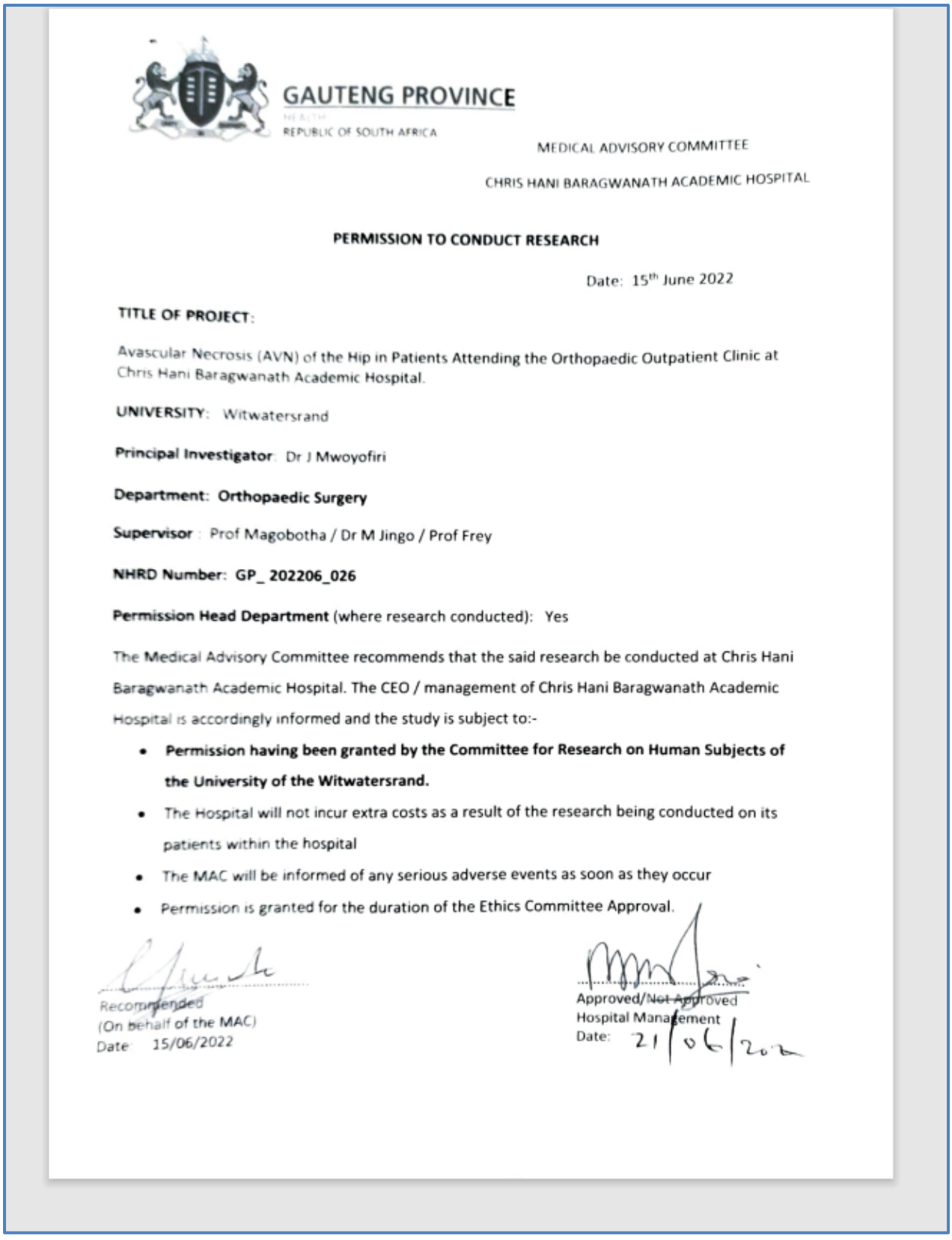
To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in April and therefore reports and re-certification will be due in the month of April each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

11/01/2023
Date

Appendix C: Hospital permission



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 15th June 2022

TITLE OF PROJECT:

Avascular Necrosis (AVN) of the Hip in Patients Attending the Orthopaedic Outpatient Clinic at Chris Hani Baragwanath Academic Hospital.

UNIVERSITY: Witwatersrand

Principal Investigator: Dr J Mwoyofiri

Department: Orthopaedic Surgery

Supervisor : Prof Magobotha / Dr M Jingo / Prof Frey

NHRD Number: GP_ 202206_026

Permission Head Department (where research conducted): Yes

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

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

Recommended
(On behalf of the MAC)
Date 15/06/2022

Approved/~~Not Approved~~
Hospital Management
Date: 21/06/2022