

# Sickle cell avascular necrosis: Prevalence and clinical profiles in a tertiary hospital northwestern Nigeria

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## Abstract

Acute painful crises are the hallmark of Sickle Cell Anaemia (SCA). However, chronic daily pain also occurs in SCA patients with a high frequency. Avascular Necrosis (AVN) of the femur is an important cause of chronic pain and adversely affects their quality of life. The aim is to determine the prevalence of AVN among SCA patients in Zaria and describe some of its clinical and laboratory features. A cross-sectional study of 58 SCA patients in steady state. Data on gender, age, presence of radiologically diagnosed AVN, number of pain crises, blood transfusions in the previous 12 months and laboratory parameters were collated. Data were analyzed using JASP version 0.11.1.0. A critical level of  $\alpha$  of 0.05 was set. Females constituted 40 out of 58 (69.0%) of the study participants. The median age was 23 (19.8, 28.0) years. AVN was present in 6 out of 58 (10.3%). There was no relationship between gender and AVN (FET,  $p=1.00$ , OR=0.889 95% CI 0.147, 5.359). There was no age difference between patients with AVN and those with-

out AVN (29.92 vs 29.45, MWU=153.500,  $p=0.956$ ). Patients with AVN had lower mean rank HCT levels (24.08 vs 30.13, MWU=123.500,  $p=0.414$ ), higher pain episodes (31.67 vs 29.25, MWU=169.000,  $p=0.747$ ), number of blood transfusions (33.42 vs 29.05, MWU=179.500,  $P=0.549$ ) and platelets (34.00 vs 28.98, MWU=183.000,  $p=0.499$ ) compared to those without AVN. Avascular necrosis is common among SCA patients in Zaria. These patients have more blood transfusions and bone pain episodes compared to those without AVN.

## Introduction

Sickle Cell Anaemia (SCA), a qualitative haemoglobinopathy, is the most common monogenic disorder worldwide. It is characterized by two different types of pain: acute and chronic pain. Acute exacerbations known as vaso-occlusive crises are the most common presentations. However, syndromes of chronic pain have been shown to be important as well.<sup>1</sup> One of the most common causes is a skeletal complication of SCA, Avascular necrosis (AVN) or osteonecrosis.

AVN occurs due to complex interactions including compromised blood flow to the bone, cell death and attempts at regeneration.<sup>2</sup> Although this may affect any bone, it commonly affects the femoral heads. This leads to chronic pain and limitation in mobility. It has been demonstrated to adversely affect quality of life.<sup>3,4</sup> This is further aggravated by limitations in effective treatment options which remain largely unsatisfactory.<sup>5</sup>

Given the protean nature of SCA and its complications it is important for locally-relevant data which will guide understanding of disease conditions to be generated. The burden of AVN among SCA patients and related clinical and laboratory changes are unknown in our environment. Hence this study sought to determine the prevalence of AVN among SCA patients and describe some of its clinical and laboratory features.

## Materials and Methods

This was a cross sectional study in which SCA patients in steady state were consecutively enrolled from the Ahmadu Bello University Teaching Hospital (ABUTH) Haematology Clinic, following acquisition of institutional ethical approval. It was estimated that, assuming a 15.9% prevalence of AVN,<sup>6</sup> a minimum sample size of 52 is required to have a 95% confidence of predicting the population prevalence with an absolute precision of 10%. However, a sample size of 58 will be required to compensate for a 10% non-response rate. Data on gender, age, presence of radiologically diagnosed AVN (X-ray), number of pain crises and blood transfusions in the previous 12 months were collated. Full blood count was conducted and data on haematocrit (HCT), white blood cell (WBC) and platelet counts were collated.

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Data were analyzed using Microsoft Excel 2016 and JASP 0.11.1.0.<sup>7</sup> Qualitative variables were summarized using percentages. The distribution of quantitative variables was assessed using skewness and kurtosis and means  $\pm$  Standard Deviation (SD) and medians [IQR (25<sup>th</sup>, 75<sup>th</sup> percentiles)] were used to summarize normally and non-normally distributed variables respectively. Mann Whitney U tests were used to assess the distribution of continuous variables across categories of qualitative variables. A critical level of  $\alpha$  of 0.05 was set.

## Results

Females constituted 40 out of 58 (69.0%) of the study participants. The median age was 23 (19.8, 28.0) years (Table 1). A summary of quantitative variables is presented in Figure 1. AVN was present in 6 out of 58 (10.3%). There was no relationship between gender and AVN (FET,  $p=1.00$ , OR=0.889 95% CI 0.147, 5.359). There was no age difference between patients with AVN and those without AVN (29.92 vs 29.45, MWU=153.500,  $p=0.956$ ). Patients with AVN had lower mean rank HCT levels compared to those without AVN (24.08 vs 30.13, MWU = 123.500,  $p=0.420$ ; Table 3).

## Discussion

The prevalence of AVN in this study is comparable to that reported by Akpan and Uboh (2018) among SCA patients in Uyo, Nigeria.<sup>8</sup> However, our findings are lower than reports from Ile-Ife, Nigeria (15.9%) and Saudi Arabia (21.7%) but higher than the reports from Enugu Nigeria.<sup>6,9,10</sup> These variations may be due to differences in study designs; the previous studies were retrospective reviews, ours was a cross sectional study. Unstudied differ-

ences in genetic make-up and environmental factors may also be responsible for these variations. This is because the number of alpha thalassemia genes have been demonstrated to have a strong relation with increasing prevalence of AVN.<sup>11</sup> Our findings suggest comparable median ages between those with and those without AVN. However, this does not imply absence of any temporal difference in occurrence because of our study design. It is worthy of note that the age box plots indicate that the participants with AVN have a higher distribution of older age compared to those without AVN. The peak incidence of AVN has been reported to be in the 21-30 year age group.<sup>6</sup> It is possible there is a delay in diagnosis due to the mode of diagnosis of AVN especially in resource constrained settings which relies predominantly on X-rays instead of Magnetic Resonance Imaging (MRI) which exhibits better discriminatory ability in early detection and staging of AVN.<sup>12,13</sup> Hence, patients may be treated repeatedly for a long-time hip pain before a definitive diagnosis becomes obvious by the X-ray.<sup>14</sup>

We have interpreted our findings in context of the interval estimates and effect sizes rather than relying solely on statistical significance. This approach is the subject of recent calls by different

**Table 1. Summary of variables.**

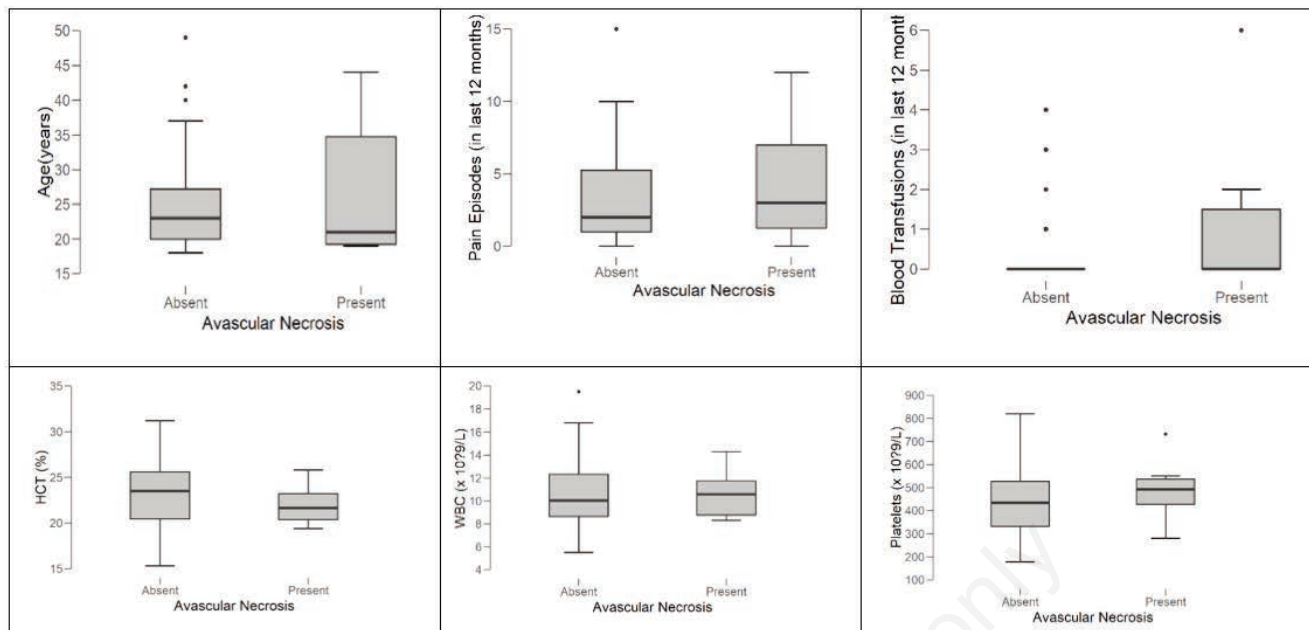
Variable	Mean (Median)
Age (years)	23.00 (19.8,28.0)
Number of pain episodes in previous 12 months	2.0 (1.0, 6.0)
Number of blood transfusions in previous 12 months	0.0 (0.0, 0.3)
Haematocrit (%)	23.0 $\pm$ 3.6
White Blood Cell (x 10 <sup>9</sup> / $\mu$ L)	0.6 $\pm$ 3.0
Platelets (x 10 <sup>9</sup> / $\mu$ L)	456.7 $\pm$ 146.1

**Table 2. Distribution of variables across avascular necrosis categories.**

Variable	AVN	Mean Rank	MWU	p
Haematocrit (%)	Absent	30.13	123.500	0.414
	Present	24.08		
White Blood Cell counts (x 10 <sup>9</sup> / $\mu$ L)	Absent	29.35	164.000	0.848
	Present	30.83		
Platelets (x 10 <sup>9</sup> / $\mu$ L)	Absent	28.98	183.000	0.499
	Present	34.00		
Age (years)	Absent	29.45	158.500	0.959
	Present	29.92		
Bone pains in the previous 12 months	Absent	29.25	169.000	0.747
	Present	31.67		
Blood transfusions in the previous 12 months	Absent	29.05	179.500	0.433
	Present	33.42		

**Table 3. Effect Sizes for Relationships of Variables Between Categories of Avascular Necrosis.**

Variables	Rank Bi-serial Correlation	95% Confidence Interval	
		Lower	Upper
Age (years)	0.016	-0.443	0.468
Pain in last 12 months	0.083	-0.387	0.519
Blood transfusion in last 12 months	0.151	-0.328	0.568
Hematocrit (%)	-0.208	-0.607	0.274
White Blood Cell count (x10 <sup>9</sup> /L)	0.051	-0.414	0.496
Platelets (x10 <sup>9</sup> /L)	0.173	-0.307	0.583



**Figure 1.** Box plots indicating medians, 25<sup>th</sup> and 75<sup>th</sup> percentiles and extreme values of continuous variables between participants with and without avascular necrosis.

groups of statisticians.<sup>15,16</sup> The interval estimates for effect sizes in this study indicate the differences may range from medium to large in the general population. These reflect the low power of the secondary analyses in this study. It is important to note that only multicentre studies will be able to give a large number of patients with AVN for adequate comparisons. Hence, we advocate for larger future multicenter studies so that larger sample sizes may unravel more precise relationships.

The absence of any relationship between gender and AVN in this study is contrary to what is expected. There is greater Nitric Oxide bioavailability and response among female SCD patients compared to males.<sup>17</sup> The links between endothelial Nitric Oxide Synthase (eNOS) and AVN with different polymorphisms in the eNOS gene have been extensively studied.<sup>18-20</sup> While the point estimate for risk suggests that female gender appears to be protective for AVN, our data also suggests the possibility of increased occurrence of AVN among females. What we do not know is whether our female SCA patient have comparable expression of NO as demonstrated in this study or whether other as yet unstudied factors may be responsible for our finding.

The relatively lower haematocrit levels and higher rates of bone pain crises among patients with AVN in this study is similar to the findings of Madu *et al.* among SCA patients in Enugu Nigeria. This phenomenon is also projected among a subset of the landmark Cooperative Study of Sickle Cell Disease cohort who had concomitant alpha thalassaemia.<sup>11</sup> This then raises the question of the need to determine the pattern of concomitant alpha thalassaemia and any effect this may have among our patients.

This study also reveals higher frequency of blood transfusion among patients with AVN. Repeated, severe haemolysis while necessitating blood transfusion lead to decreased bioavailability of NO due to the mopping up effects of cell-free haemoglobin and perturbations as a result of the action of arginase on arginine. The ensuing vasculopathy may contribute the evolution of AVN.<sup>21</sup>

## Conclusions

AVN is common among SCA patients in Zaria. These patients have more blood transfusions and bone pain episodes as well as lower haematocrit levels and higher platelet counts compared to those without AVN.

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