

# Avascular necrosis in sickle cell (homozygous S) patients: Predictive clinical and laboratory indices

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## Abstract

**Background:** Pathogenetic mechanism as well as laboratory and clinical correlates of osteonecrosis in sickle cell have not been fully investigated. The aim of this study is to investigate the predictive value of the steady state white cell and platelet count as well as the frequency of bone pain crisis per annum to detect sickle cell patients who will eventually develop avascular necrosis (AVN).

**Patients and Methods:** A 5 year retrospective analysis of 122 homozygous S (HbSS) patients, aged 6-49 years (mean age  $24.7 \pm 7$  years), out of which 16 patients (13.1%) had developed AVN within the years under review.

**Results:** The prevalence of AVN in sickle cell patients was determined to be 13.1 per 1000. The steady state white cell count, platelet count, frequency of bone pain crisis and hematocrit, was compared in patients that develop AVN and those who had not over the period. Only the steady state platelet count was found to differ significantly ( $P = 0.011$ ) between these two patient groups and to correlate positively (Pearson correlation coefficient =  $-0.251$ ) with development of AVN. The hematocrit, white cell count, and frequency of bone pain crisis were found neither to differ significantly nor correlate with the development of AVN.

**Conclusion:** In conclusion, patients with a raised steady state platelet count may have a higher tendency to develop AVN and may require closer orthopedic review and prophylactic intervention.

**Key words:** Avascular necrosis, homozygous S, platelet count, sickle cell anemia, white cell count

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## Introduction

Avascular necrosis (AVN) is a debilitating and life-changing complication of sickle cell disease and its prevalence ranges from 3.2% to 26.7% in this group of patients.<sup>[1-3]</sup> The prevalence of healthy carriers (sickle cell trait) ranges between 10% and 40% across equatorial Africa and decreases to between 1% and 2% in Northern Africa and less than 1% in Southern Africa.<sup>[4]</sup> In West African countries such as Ghana and Nigeria, the frequency of the carrier state is 15-30% while in East African countries such as Uganda and Tanzania, it shows wide variations of up to 45% in some areas.<sup>[5,6]</sup> In Nigeria, with an estimated carrier prevalence of 24%, 20/1000 births are estimated to be affected by sickle cell disease (SCD) resulting in 150,000 children with

SCD born annually in Nigeria. About 300,000 children are born annually world-wide with sickle cell disease with Nigeria accounting for one-third of this population.<sup>[3]</sup> About 1.2 million people are affected while India has the highest number of affected people in any one country.

AVN is a well-recognized complication of sickle cell disease observed by Graham as early as 1924. The exact mechanism of this complication has not been fully explained; however, micro-vascular occlusion from hypoxia induced erythrocyte sickling, along with extra-vascular compression of the intra-osseous blood supply caused by marrow hyperplasia

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and hypertension results in ischemia, which culminates in bone infarction.<sup>[7]</sup> Raised hematocrit, low hemoglobin F, co-existence of alpha thalassemia trait and frequent episodes of vaso-occlusive crisis have all been shown to be positively correlated with AVN<sup>[7-9]</sup> The importance of blood components, such as white cells and platelets in the pathogenesis of vaso-occlusion and severity of sickle cell disease has been reported. It is then necessary to investigate how these parameters relate with prevalence of complications such as AVN.

Previous studies have all been prospective and have compared values in sickle patients with healthy controls while others have been cross-sectional and focused on one of assessment of parameters between sickle cell patients who already had or did not have AVN,<sup>[10,11]</sup> in which case it may be difficult to discern whether these are the causes or effects of this complication. The importance of a retrospective study in this instance provides information on the pre-morbid parameters as well as a better epidemiological assessment.

Predictive laboratory or clinical parameters, which correlate positively will help the physician to tailor preventive measures toward at risk patients. Furthermore, these may serve as targets for prophylactic therapeutic interventions, whose advantage cannot be underestimated in reducing the incidence of this life-long debilitating complication.

## Patients and Methods

This was a 6 year retrospective study of all patients seen at the sickle cell clinic of the University of Nigeria Teaching Hospital from 1<sup>st</sup> of January 2005 to the 1<sup>st</sup> of January 2010. Approval was obtained from the Ethics Committee of the hospital. Data at steady state was extracted from the hospital records. Patients who were not homozygous S (HbSS) on hemoglobin electrophoresis were excluded from the study. Data analyzed included age, sex, presence AVN, frequency of bone pain crisis per annum and steady state hematocrit, white cell, and platelet counts. Furthermore, the case note was used to ascertain those that had developed AVN in the period under review. Diagnosis of AVN was confirmed by the Radiologist and Orthopedic Surgeon using the plain radiographs of the affected hip. Excluded from the study were those who had developed AVN at presentation (this was to avert a possible confounding effect of AVN-associated increase in these parameters) or were not HbSS. The correlation between frequency of vaso-occlusive crisis, platelet, and white cell count and development of AVN was then computed.

## Statistics

The aim of this study is to determine the predictive value of a high white cell and platelet count with regards to the risk of developing AVN in this patient group. Other clinical

and laboratory variables; number of crises per annum and hemoglobin concentration were also collated. Pearson's correlation co-efficient (two-tailed) was then obtained for each variable and presented in a tabular form. The *P* value was taken for all values < 0.05. Analysis was carried out with the Statistical Package for the Social Sciences (SPSS United Kingdom 2009) for windows version 17.0 package. Ethical clearance was obtained from the University of Nigeria Teaching Hospital Ethical Committee.

## Results

The case notes of 122 patients who were seen in the clinic during the period under review were pooled and relevant data were extracted. They were 69 males (56.6%) and 53 (43.4%) females, giving a ratio of 1.3:1. The patients were aged 6-49 years at presentation with a mean age of  $24.7 \pm 7.1$  years and median age of 23 years. A total of 58 (47.5%) patients were aged 21-30 years while 37 (30.3%) patients were aged 11-20 years. A total of 23 (18.9%) were aged 31-40 years while two (1.6%) patients each were aged 10 years or below and 41-50 years respectively. The prevalence of AVN was found to be 13.1/1000 amongst sickle cell patients.

The mean white cell count was observed to be  $13.5 \pm 8.8 \times 10^9/L$  and median value was  $11.8 \times 10^9/L$  ( $n = 101$ ), the mean hematocrit was found to be  $22 \pm 5.5\%$ , with a median value of 22% ( $n = 83$ ), and the mean platelet count was  $326 \pm 145 \times 10^9/L$ , and the median was  $328 \times 10^9/L$  ( $n = 114$ ). A total of 79 of the respondents had bone pain crises in the last 5 years and the average frequency was 3.8 episodes/annum. Frequency of bone pain crises was plotted against white cell count in those that had AVN and those that had none [Figure 1], and shows no graphical relationship between a high white cell count and pre-disposition to AVN. Figure 2 shows a similar boxplot of the frequency of bone pain against platelet count in both

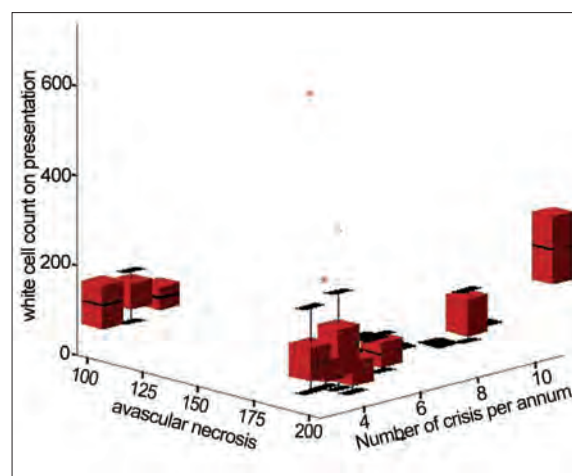
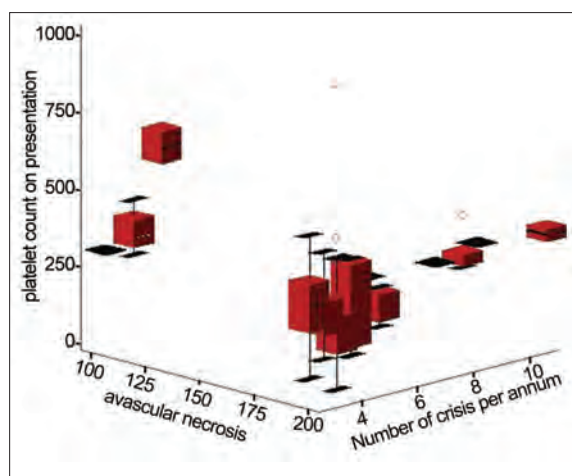


Figure 1: Relationship between white cell count/frequency of crises/avascular necrosis



**Figure 2:** Relationship between platelet count/frequency of crises/ avascular necrosis

patient that did and did not develop AVN and reveals a positive relationship between high steady state platelet count and pre-disposition to AVN. Correlation co-efficient was evaluated in both patient groups with respect to their steady state white cell and platelet count as well as frequency of bone pain crises per annum and is shown in Table 1.

A total of 23 patients (18.9%) were found to have bone and joint involvement in sickle cell disease in this study. 9 (39.1%) were females while 14 (60.9%) were males. Sixteen patients (13.1%) had AVN of the hip involving 19 hips with 3 patients having bilateral hip involvement. AVN was not noticed in any other joint. Left hip affection was more common (52.6%) than right hip involvement. Majority (73.7%) of the cases of AVN of the hip was seen in patients aged 21-30 years. Only three cases were noted in patients aged 31-40 years. The rest occurred in patients aged 11-20 years.

## Discussion

The current patho-physiologic mechanism of vaso-occlusion in sickle cell disease has been found to involve the white cells and platelets as well as the expression of their inter-cellular adhesion molecules. The relationship between the white cell and platelet counts with disease severity in sickle cell has also been observed in previous studies.<sup>[12]</sup> However, the relationship between the incidence of illness complications such as AVN and patient's clinical parameters remain vague. A high platelet count was observed to positively correlate with a tendency to develop AVN. The role of platelets in the pathogenesis of vaso-occlusion has been described; however, chronic complications like AVN, may involve irreversible thrombogenesis. It is known that depletion of platelets as well as white cell count, result in reduction of frequency of bone pain. The importance of our findings lies in the possible prevention of AVN using platelet-depleting or regulating agents.

**Table 1: Haematological Indices in sickle cell patients in cohort**

Haematological Index	Has AVN	No AVN	Pearson correlation coefficient and T test (2-tailed)
Mean Platelet count (x 10 <sup>9</sup> /L)	(n=8) 450±182	(n=93) 315±138	-0.251 (0.011)*
Mean White Cell count (x 10 <sup>9</sup> /L)	(n=9) 10.9±4.1	(n=105) 13.7±9.0	0.086 (0.363)
Mean Haematocrit (%)	(n=6) 24±3.6	(n=77) 22±5.6	-0.099 (0.374)
Number of crises per annum	(n=8) 3.8±1.5	(n=71) 3.7±4.0	-0.007 (0.953)

\*Significant values <0.05

Other factors, which had been associated with development of AVN include a high hematocrit;<sup>[13]</sup> however, this was not supported by the findings of our study as well as a study done by<sup>[1,11]</sup> Disease severity has been expressed in most studies to correlate with a raised white cell count;<sup>[5,6]</sup> however, it seems development of some of the complications of sickle cell like AVN as well as cerebrovascular accidents do not have a direct relationship to it. Our study did not reveal any significant difference between the rise in white cell count and development of AVN.

The group with AVN had a higher frequency of bone pain crisis, though this was not significantly different from those who did not. This is not supported by previous study; however, this may be an indication that AVN in sickle cell has a different pathogenetic mechanism from vaso-occlusion. The frequency of bone pain has been observed to be an indicator of disease severity, in previous studies done the number of patients were less than that of this study and might not have been representative of the overall patient population.

This study has shown a close relationship between a high steady state platelet count and the development of AVN. Further studies are needed to investigate the thrombotic occlusion seen in AVN as it may not necessarily be vaso-occlusive. Possible therapeutic intervention may be targeted at the platelet-thrombin component as a preventive modality for patients at risk.

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MA and MK designed the study and take major responsibility for the study, KU and IK did the statistical analysis while DA and OU collated the data.

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