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Avascular Bone Necrosis in Pediatric Patients with Sickle Cell Disease in Basrah, Iraq

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Abstract:

BACKGROUND: Avascular necrosis (AVN) is regarded as a manifestation of severe sickle cell disease (SCD), with the femoral head being the most affected.

OBJECTIVES: The main objectives of this study were to look for the frequency of AVN in pediatric patients with SCD, evaluate the clinical pattern and severity of AVN, and study the possible risk factors associated with AVN.

MATERIALS AND METHODS: A cross-sectional study has been conducted on SCD patients, aged 6–18 years, who visited the Basrah Center for Hereditary Blood Diseases from the first of February 2021 to August 2021. Patients were screened for AVN by hip plain radiography and magnetic resonance imaging. The modified Ficat-Arlet staging system was used to classify different stages of AVN.

RESULTS: The total number of screened patients was 291; 193 (66.3%) had sickle cell anemia, 71 (24.4%) with S/β^0 thalassemia, 21 (7.2%) with S/β^+ thalassemia, and 6 (2.1%) had S/D disease. Fifty-eight (19.9%) patients were found to have different stages of AVN; 7 (12.1%) were asymptomatic and 51 (87.9%) were symptomatic. The logistic regression analysis has revealed that frequent vaso-occlusive crises requiring hospitalization ($B = 1.576$, $P = 0.003$), acute splenic sequestration crises ($B = 1.256$, $P = 0.003$), homozygous sickle hemoglobin genotype ($B = -0.208$, $P = 0.001$), and low reticulocyte count ($B = 1.452$, $P = 0.027$) are significant variables associated with AVN.

CONCLUSION: AVN was reported in a significant percentage of pediatric patients with SCD and was associated with selected indicators of disease severity. Further studies that evaluate the natural history, progress of AVN, and variations in selected variables over time like reticulocytes and the co-inheritance of α-thalassemia are important.

Keywords:

Avascular bone necrosis, pediatric patients, sickle cell disease

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Introduction

Sickle cell disease (SCD), inherited by a single gene mutation, is considered among the most common serious genetic diseases globally. The disease adversely affects the health of children due to its associated complications that could be acute or chronic.[1]

Despite the chronic nature of the disease, however, patients may present with various acute SCD-related complications such as acute painful episodes, acute chest syndrome (ACS), and priapism. The frequency and severity of these complications differ from one patient to another, within the same patient over time, in different parts of the world, and also differ with the patient's age and sex.[2]

Bone involvement occurs frequently in SCD and is regarded as the most common clinical presentation of this condition. It can be acute as painful vaso-occlusive crises (VOC) and infections (septic arthritis

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and osteomyelitis) or can be chronic and progressive in nature as in avascular necrosis (AVN).[3] Chronic bone damage is a considerable cause of long-term morbidity in these patients.[4]

AVN or osteonecrosis results from transient or permanent inadequate or interruption of blood supply to the bones and is regarded as a manifestation of severe SCD, with the femoral head being the most affected site. Several predisposing factors for AVN have been identified, including genetic factors,[5] coexistence of α-thalassemia trait,[6] VOCs and hospitalizations,[7,8] fetal hemoglobin (HbF) level,[7,9] white blood cell (WBC) count, platelets, hemoglobin and hematocrit levels,[6-8,10] and low bone density.[11]

If AVN is not treated, it can be severely crippling and may lead to extreme pain, loss of joint structure (joint degeneration), and eventually to loss of joint function. However, the treatment of AVN is not standardized.[12] Important challenges in managing children with SCD and AVN of the femoral head are the late diagnosis due to vague and nonspecific symptoms initially and the presence of various perioperative challenges, like the preoperative planning for exchange blood transfusion.[13]

The survival of patients with SCD has greatly improved because of many preventive and therapeutic measures, including newborn screening, prophylactic penicillin, hydroxyurea (HU) therapy, chronic red blood cell (RBC) transfusions, and transcranial Doppler screening.[14,15] However, few have focused on chronic SCD complications, specifically AVN. Therefore, we conducted this study to look for the frequency of AVN in pediatric patients with SCD, evaluate the main sociodemographic, clinical pattern, and severity of AVN compared to SCD patients without AVN, and study the possible risk factors associated with AVN.

Materials and Methods

Patients

This analytical cross-sectional study was conducted on pediatric patients with SCD who have been registered at the Basrah Center for Hereditary Blood Diseases (CHBD).

A total of 291 patients with SCD who consulted the CHBD from the first of February 2021 to the end of August 2021 were recruited in the study, their ages ranged from 6 to 18 years, and they were selected by a stratified random sampling method.

A specially designed questionnaire for the purpose of the study was used, which included sociodemographic variables, disease-related variables, and past medical history.

Full clinical data were obtained, including SCD-related complications like acute splenic sequestration crises (ASSC), ACS, stroke, hepatobiliary complications (hepatitis and gallstone), and musculoskeletal complications such as osteomyelitis as well as the use of HU.

The physical examination included general examination, growth measures, and systemic examination. For all patients enrolled in this study, the weight was measured wearing light clothes, the height was taken barefoot, and the body mass index (BMI) was calculated. The BMI *Z* scores (BMIZ) for age were calculated against the 2007 World Health Organization references for ages 5–19 years. Subjects were classified to have severe thinness (<−3 standard deviation [SD]), thinness (<−2 SD), (−2–+2 SD) normal, (>+2–+3 SD) overweight, and obesity (>+3 SD).[16,17]

Patients excluded from the study included those with SCD but are not registered at the CHBD, patients with other hemoglobinopathies like homozygous hemoglobin D or C disease, patients with SCD who are <6 years and more than 18 years old, patients with SCD in crisis at the time of the study (acute painful episode and ASSC), and those who have fever or coexisting bacterial infections.

An informed consent was acquired from patients and/or one of their parents for participation in the project.

The study has been endorsed by the Scientific and Ethical Committee of the College of Medicine, University of Basrah (Ref. Number 0304111-2020, 4S/343 on November 4, 2020), and Basrah Health Directorate.

Severe disease was defined as frequent VOC requiring hospitalization ≥3/year, blood transfusions ≥3/year, frequent hospitalizations ≥3/year, or at least one episode of stroke, ACS, or AVN of the bone.[18,19]

Methods

Laboratory investigations

- Complete blood count and reticulocyte count
- Hemoglobin concentration, hematocrit (HCT), RBC count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), WBC count, and platelets count were evaluated using Automated Hematology Analyzer (Sysmex XN-350, Japan)
- Hemoglobin components quantitation was done using high-performance liquid chromatography, ADAMS HA-8180T Analyzer (ARKRAY, Inc., Kyoto, Japan)
- Lactate dehydrogenase (LDH) enzyme assay was done using Abbott® ARCHITECT C4000 Biochemistry Analyzer, USA.

Diagnosis of avascular necrosis

The patients were screened for AVN by hip plain radiography (X-ray), and then magnetic resonance imaging (MRI) was requested following an abnormal bone image to confirm the diagnosis and staging. The MRI was also done for cases with persistent symptoms (e.g., pain, limping) with a normal X-ray to confirm/exclude the diagnosis of femoral head AVN.

The MRI was done using 3 Tesla Achieva MRI Machine (Philips/Japan); spin echo T1- and T2-weighed images and T2 FATSAT sequences in coronal and axial planes in 4-mm thick sections were obtained.

The modified Ficat-Arlet staging system was used to classify different stages of AVN, where clinical features, plain radiography, and MRI are used in combination to stage AVN.[20,21]

Statistical analysis

Data were processed and analyzed using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). The Chi-squared test and Fisher's exact test were used to assess categorical variables (presented as numbers and percentages). The independent *t*-test was used for quantitative comparison between two means of different samples.

Logistic regression analysis was done to look for the potential AVN-associated risk factors.

Results

The total number of screened patients was 291; 193 (66.3%) had SCA, 71 (24.4%) with S/β^+ thalassemia, 21 (7.2%) with S/β^+ thalassemia, and 6 (2.1%) had S/D disease. Fifty-eight (19.9%) patients were found to have different stages of AVN. The frequency of AVN among patients with different types of SCD was the highest among those with S/β^0 thalassemia 25 (35.2%), followed by S/D disease 1 (16.7%) and SCA 31 (16.1%), while those with S/β^+ thalassemia had the lowest frequency 1 (4.8%), $P < 0.05$.

The age of SCD patients with AVN was significantly higher than children without AVN, $P < 0.05$ [Table 1], while no significant differences in sex and residence were reported ($P > 0.05$). However, a significantly higher percentage of SCD patients with AVN was found to be illiterate compared to those without AVN, $P < 0.05$.

Hospitalization ≥3/year, recurrent VOC ≥3/year, and frequent blood transfusion ≥3/year were reported in significantly higher frequencies in patients with AVN compared to those without AVN, $P < 0.05$. In addition, ASSC, stroke, and HU use were also found to be significantly more frequent in AVN patients, $P < 0.05$, [Table 2].

No significant differences were reported in jaundice, pallor hepatomegaly, and splenomegaly among both groups, $P > 0.05$. When patients of both groups were categorized, height for age *Z* score and BMIZ distributions did not show significant statistical differences between those with and without AVN, $P > 0.05$. None of the SCD patients of both groups was found to be severely thin or obese, [Table 3].

Hemoglobin, HCT, MCV, MCH, and MCHC were significantly higher in AVN patients compared to patients who did not have AVN, $P < 0.05$. On the other hand, reticulocyte count and HbF were significantly lower levels in AVN patients, $P < 0.05$, [Table 4]. The Hb/HCT ratio, WBC, neutrophils, platelets, and LDH did not show significant differences in patients with and without AVN, $P > 0.05$.

Out of 58 patients with AVN, 7 (12.1%) were asymptomatic and 51 (87.9%) were symptomatic. Pain was the most common symptom in 27 (53%), followed by pain and limping in 17 (33.3%) and limping only in 7 (13.7%) patients. No significant difference was reported among male and female patients with AVN concerning the frequency of pain and limping, $P > 0.05$. Two patients had shortening of the limb in addition to limping. The left hip was the most common site affected by AVN in both genders 28 (48.3%), followed by both hips 14 (24.1%), and then the right hip in only 12 (20.7%). Involvement of the spines was reported in 3 (5.2%) patients and one patient had right hip and right shoulder involvement. No significant difference in the site of AVN was identified between male and female patients, $P > 0.05$.

Most patients with AVN were diagnosed during stage 3 according to the FICAT classification 25 (43.1%) [Figure 1], followed by stage 2 (16 [27.6%]) and stage 1 (13 [22.4%]). Only 4 (6.9%) were with stage 4 disease. Stages of AVN reported did not show significant variation in relation to sex, $P > 0.05$.

The logistic regression analysis has shown that frequent VOC requiring hospitalization, ASSC, having

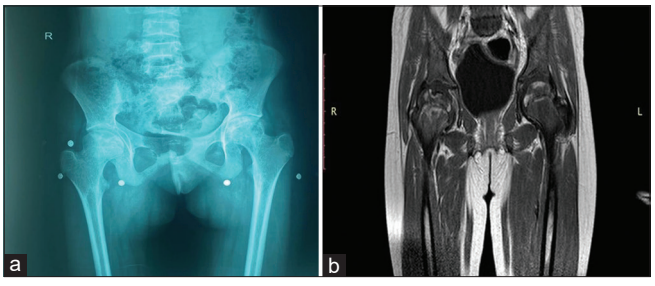

Figure 1: Stage 3 avascular necrosis. (a) plain radiography, (b) MRI of the hip. Both show early collapse and crescent sign (subchondral lucency)

Table 1: Demographic characteristics of sickle cell disease patients in relation to avascular necrosis

Variable	SCD patients		Total (*n*=291), *n* (%)	*P*
	AVN (*n*=58), *n* (%)	Without AVN (*n*=233), *n* (%)		
Age (years)				
6–12	32 (55.2)	172 (73.8)	204 (70.1)	0.006*
13–18	26 (44.8)	61 (26.2)	87 (29.9)	
Mean	12.3±2.3	10.6±3.1	10.9±3.1	0.0001**
Gender				
Male	35 (60.2)	145 (62.2)	180 (61.9)	0.790*
Female	23 (39.7)	88 (37.8)	111 (38.1)	
Residence				
Center	18 (31.0)	69 (29.6)	87 (42.6)	0.833*
Periphery	40 (69.0)	164 (70.4)	204 (70.1)	
Education				
Illiterate	26 (44.8)	66 (28.3)	92 (31.6)	0.006*
At school	32 (55.3)	167 (71.7)	199 (68.4)	

*Chi-square test; **Student's *t*-test. AVN=Avascular necrosis; SCD=Sickle cell disease

Table 2: Selected clinical characteristics of studied sickle cell disease patients

Variable	SCD patients		Total (*n*=291), *n* (%)	*P*
	AVN (total *n*=58), *n* (%)	Without AVN (total *n*=233), *n* (%)		
VOC required hospitalization (*n*/year)				
None	6 (10.3)	113 (48.5)	119 (40.9)	0.001*
<3	6 (10.3)	83 (35.6)	89 (30.6)	
≥3	46 (79.3)	37 (15.9)	83 (28.5)	
Hospitalization (*n*/year)				
None	10 (23.3)	143 (74.9)	153 (65.4)	0.001*
<3	8 (18.6)	39 (20.4)	47 (20.1)	
≥3	25 (58.1)	9 (4.7)	34 (14.5)	
Type of surgery				
Splenectomy	7 (12.1)	27 (11.6)	34 (11.7)	0.256**
Cholecystectomy	3 (5.2)	6 (2.6)	9 (3.1)	
Both	3 (5.2)	5 (2.1)	8 (2.7)	
Tonsillectomy	1 (1.7)	0	1 (0.3)	
No surgery	44 (75.9)	195 (83.7)	239 (82.1)	
Frequency of blood transfusion (*n*/year)				
No	13 (22.4)	83 (35.6)	96 (33.0)	0.001*
1–2	5 (8.6)	71 (30.5)	76 (26.1)	
≥3	40 (69.0)	79 (33.9)	119 (40.9)	
ASSC				
Yes	31 (53.4)	68 (29.2)	99 (34.0)	0.001*
No	27 (46.6)	165 (70.8)	192 (66.0)	
ACS				
Yes	9 (15.5)	24 (10.3)	33 (11.3)	0.262*
No	49 (84.5)	209 (89.7)	258 (88.7)	
Stroke				
Yes	11 (19.0)	11 (4.7)	22 (7.6)	0.001*
No	47 (81.0)	222 (95.3)	269 (92.4)	
Hepatitis				
Yes	0	9 (3.9)	9 (3.1)	0.128**
No	48 (100.0)	224 (96.1)	268 (96.9)	
HU				
Yes	38 (65.5)	78 (33.5)	116 (39.9)	0.001*
No	20 (34.5)	155 (66.5)	175 (60.1)	

*Chi square test; **Fisher's exact test. AVN=Avascular necrosis; SCD=Sickle cell disease; VOC=Vaso-occlusive crises; ASSC=Acute splenic sequestration crises; ACS=Acute chest syndrome; HU=Hydroxyurea

Table 3: Clinical findings of sickle cell disease patients with and without avascular necrosis

Variable	SCD patients		Total (*n*=291), *n* (%)	*P*
	AVN (*n*=58), *n* (%)	Without AVN (*n*=233), *n* (%)		
Pallor				
Yes	34 (58.6)	127 (54.5)	161 (55.3)	0.573*
No	24 (41.4)	106 (45.5)	130 (44.7)	
Jaundice				
Yes	3 (5.2)	11 (4.6)	14 (4.8)	0.886**
No	55 (94.8)	222 (95.3)	277 (95.2)	
Hepatomegaly				
Yes	3 (5.2)	11 (4.6)	14 (4.8)	0.886**
No	55 (94.8)	222 (95.3)	277 (95.2)	
Splenomegaly				
Yes	33 (56.9)	102 (43.8)	135 (46.4)	0.073*
No	25 (43.1)	131 (56.2)	156 (53.6)	
HAZ score				
Normal	41 (70.7)	157 (67.4)	198 (68.0)	0.418**
Stunting	14 (24.1)	69 (29.6)	83 (28.5)	
Severe stunting	2 (3.4)	3 (1.3)	5 (1.7)	
Tall	1 (1.7)	4 (1.7)	5 (1.7)	
BMIZ score				
Normal	55 (94.8)	197 (84.5)	252 (86.6)	0.109**
Thinness	3 (5.2)	31 (13.3)	34 (11.7)	
Overweight	0	5 (2.1)	5 (1.7)	

*Chi-square test; ***P* value was assessed by Fisher's exact test. AVN=Avascular necrosis; SCD=Sickle cell disease; HAZ score=Height for age *Z* score; BMIZ=Body mass index *Z* score

Table 4: Laboratory data of patients with and without avascular necrosis

Variables	SCD patients, mean±SD		Total (*n*=291), mean±SD	*P**
	AVN (total *n*=58)	Without AVN (total *n*=233)		
Hb (g/dL)	8.96±1.51	8.46±1.63	8.56±1.61	0.036
HCT	26.16±5.36	24.33±4.96	24.70±5.09	0.015
Hb/HCT ratio	0.342±0.04	0.350±0.07	0.348±0.07	0.459
MCV (fL)	87.83±13.12	80.56±13.07	82.04±13.38	0.0001
MCH (pg)	30.16±5.40	29.71±20.89	29.80±18.84	0.873
MCHC (g/dL)	44.23±53.04	33.98±2.72	36.02±23.99	0.003
WBC ($\times10^3/\mu L$)	11.35±5.13	11.47±6.68	11.44±6.39	0.899
Neutrophils (%)	53.75±12.08	51.82±11.46	52.20±11.59	0.258
Platelets ($\times10^3/\mu L$)	407.69±194.20	355.31±195.57	365.75±196.09	0.069
Retics (%)	6.73±4.48	12.20±5.99	11.11±6.12	<0.001
HbF (%)	16.28±7.94	20.92±10.69	20.00±10.35	0.002
LDH (U/L)	397.17±182.62	402.31±193.58	401.29±191.15	0.850

*Independent sample *t*-test. AVN=Avascular necrosis; Hb=Hemoglobin; HCT=Hematocrit; MCV=Mean corpuscular volume; MCH=Mean corpuscular Hb; MCHC=Mean corpuscular Hb concentration; WBC=White blood cells count; Reics=Reticulocytes; HbF=Fetal Hb; LDH=Lactate dehydrogenase; SD=Standard deviation

homozygous hemoglobin S (HbS) genotype, and low reticulocyte count are significant variables associated with AVN, $P < 0.05$, [Table 5].

Table 5: Potential risk factors for avascular necrosis

Variable	*B*-coefficient	OR	95% CI		*P*
			Lower	Upper	
VOC	1.576	4.837	1.726	13.552	0.003
ASSC	1.256	3.511	1.553	7.942	0.003
Retics count	−0.208	0.812	0.740	0.891	0.001
Hb SS	1.452	2.410	1.653	7.101	0.027

CI=Confidence interval; VOC=Vaso-occlusive crises; ASSC=Acute splenic sequestration crises; Retics=Reticulocytes; Hb SS=Homozygous sickle hemoglobin; OR=Odds ratio

Discussion

AVN is one of the serious complications in SCD; however, the pathogenesis of the disease has not been fully determined.[8]

In this study, the frequency of AVN in pediatric patients with SCD was 19.9%, and indicators of disease severity (such as VOC requiring hospitalization and ASSC), homozygous HbS genotype, and low

reticulocyte count are significant variables associated with AVN.

The frequency of AVN among our patients is lower than that reported by Adekile *et al*., in Kuwait (27.5%).[22] A more recent study in Kuwait reported an overall prevalence of 21.3% among different age groups: 6.8% among those ≤ 16 years of age and 39.9% for those older than 16 years.[6]

Matos *et al*., in Brazil, reported AVN in 11.1% of SCD patients under the age of 21 years,[9] while Al Fadhali *et al*. reported that the prevalence of AVN in young patients with SCD in Oman was 2.8%, and they attributed this low prevalence to the possibility of underdiagnosis of patients with asymptomatic stage 1 and 2.[23] In Nigeria, Ofakunrin *et al*. found that the percentage of AVN increased from 1.9% to 17.3% in patients aged 5–9 years and 15–17 years, respectively.[24] These differences in AVN frequencies in pediatric patients with SCD can be attributed to genetic factors, disease severity, and different age groups included in various studies.[6,25,26]

The majority of AVN cases in the current study were reported in patients with S/β^0 thalassemia and SCA. Mahadeo *et al*., in the USA, reported a prevalence of 12.4% for all genotypes; 14.2% among SCA and Sβ^0 thalassemia and 9.2% for S/C patients,[27] while Adekile *et al*., in Kuwait, did not report a significant difference in the frequency of AVN and among patients with SCA, S/β thalassemia, and S/D genotypes.[22]

Homozygous HbS was found to be an independent risk factor for AVN in this study. Among patients with SCD, one of the risk factors for AVN is homozygous HbS with co-inheritance of the α-thalassemia trait (with relatively high Hb).[28]

The analysis of sociodemographic risk factors for AVN in patients with SCD revealed that the age of patients with AVN was significantly higher than those without AVN. This is in agreement with the results of Madu *et al*. in Nigeria, who reported that the percentage of AVN was 30.3% in patients aged 11–20 years.[10] Adesina *et al*., in the USA, also reported a similar finding.[14]

The frequency of AVN was not significantly different between males and females. Al-Jafar *et al*., in Kuwait, reported a similar finding.[29] This finding is in contrast to that found by Mahadeo *et al*., in the USA,[27] and Adesina and Neumayr, in the USA, also who reported that male gender is a risk factor for AVN in SCD patients.[28]

The current study demonstrates that a higher percentage of SCD with AVN were found to be illiterate compared to those who have no AVN. This can be related to the disease severity and associated complications and psychosocial problems which lead to frequent school absences and eventually leaving school.[30]

Many indicators of disease severity were found in significantly higher frequencies among the AVN group compared to patients without AVN. However, regression analysis showed that only recurrent VOC requiring hospitalizations ≥3/year and ASSC were associated with AVN in this study. Shayeb *et al*., in the USA, found that frequent VOC episodes (>5 episodes during 5 years) in children with SCD strongly predict symptomatic AVN, and they recommended MRI screening for these children for any clinical symptomatology.[31] Adekile *et al*., in Kuwait, also found that SCD children with AVN have been hospitalized for VOC in the preceding 3 years significantly more than those without AVN.[7] However, Madu *et al*., in Nigeria, did not find a significant association of painful episodes with AVN.[10]

With recurrent painful VOCs, the blood flow to the joints will be compromised with progressive occlusion of the microcirculation within the bones, especially the femoral head, because of the lack of collateral blood flow for the head of the femur, therefore, increasing the risk of AVN.[28]

HU therapy was also found in a significantly higher frequency of AVN patients. A similar finding was found by Mahadeo *et al*.[27] and Yu *et al*., in the USA.[32] The association of HU therapy with AVN was attributed to that HU therapy could be a representative of disease severity, and based on this, these SCD patients on HU would be expected to have a higher rate of developing AVN. Furthermore, HU is well known to increase the HbF and hematocrit and this will lead to elevation in blood viscosity and increased sickling in the bone microcirculation.[27] However, Adesina and Neumayr did not find an association between HU use and AVN,[28] while Ferreira *et al*., in Brazil, reported that most AVN cases were reported in those who were not on HU therapy.[33]

The mean Hb, HCT, MCV, MCH, and MCHC were significantly higher in patients with AVN than those without AVN, while the reticulocyte count and HbF were significantly lower although only reticulocyte count was found to be a predictor of AVN in our patients. The higher red cell indices in the AVN group could be attributed to the high frequency of α thalassemia among SCD patients in Basrah (18.4%).[34]

Increased hematocrit in patients with AVN was also reported by Mahadeo *et al*., in the USA.[27] However, Adekile *et al*. mentioned that there was no

significant influence of HbF, LDH, Hb, or hematocrit on AVN development.[22] Madu *et al*. also did not report a significant correlation of hematocrit and WBCs with AVN.[10] Although the factors involved in the pathogenesis of AVN are not clear, an increased blood viscosity has been regarded as a potential risk factor.[35]

Although the mean of HbF was higher in the group of patients without AVN than the AVN group, regression analysis did not reveal that low HbF is a predictor of AVN. Adekile *et al*. also reported such a finding.[7] Other studies revealed that low HbF level is associated with a higher probability of intravascular sickling and high viscosity which lead to bone necrosis.[8,36] The level of HbF in patients with SCD is determined genetically, and a high level of HbF is protective against painful crisis, bone necrosis, leg ulcers, and ACS and improves survival; therefore, a high level of HbF is associated with less severe disease, as cells that carry high HbF levels have longer survival than other cells that contain only HbS, and a high level of HbF also affects the rate and extent of the polymerization of HbS.[37]

In this study, there was no specific pattern of presentation, in terms of pain type and pain site, among male and female patients with AVN.

The left hip was the most common site affected by AVN in both genders, and about one-quarter of patients had both hips affected. This finding differs from that of Mahadeo *et al*., in the USA, who reported bilateral hip osteonecrosis in 56% of children and adolescents with SCD,[27] and Mallet *et al*., in France, who reported bilateral hip involvement in 47% of pediatric patients with SCD.[13]

Most patients with AVN were diagnosed during stage 3, followed by stage 2. This finding is consistent with the findings of Mallet *et al*., who reported stage 3 in 52% of patients, followed by stage 2 (36%),[13] while Elalfy *et al*. studied SCD with AVN from Egypt and Oman and found that 19.1% had stage 2, 20.6% had stage 3, and 25% of patients were at stage 4 disease.[38] In Nigeria, Akinyoola *et al*. found that most patients have stage 4 AVN (52%), followed by stage 2 disease (28%),[8] and Ofakunrin *et al*. reported that 75.8% of the children have been diagnosed at late stages of the disease.[24] The difference can be explained by the different screening tools used in different study populations (plain radiography, MRI, or both), different scoring systems, and whether different centers screen children with SCD for AVN early and routinely.

One limitation of this study is that it was a cross-sectional study, where the natural history, the progress of AVN, and variations in selected variables over time like reticulocytes were not evaluated. Furthermore, the co-inheritance of α-thalassemia in the screened patients was not studied.

Conclusion

Avascular bone necrosis was reported in a significant percentage of pediatric patients with SCD, most of them in stages 2 and 3. Selected indicators of disease severity, homozygous HbS genotype, and low reticulocyte count are significant variables associated with AVN. Regular screening of all patients with SCD of different age groups for AVN, starting at the age of 6 years, reducing the frequency and optimum treatment of VOC, expanding the regular use of HU and educating patients and their families about the role of HU in cases of severe SCD, are important for the prevention and early detection of AVN.

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Conflicts of interest
There are no conflicts of interest.

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