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Hemoglobin to Hematocrit Ratio: The Strongest Predictor of Femoral Head Osteonecrosis in Children with Sickle Cell Disease

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Abstract

Background—Femoral head osteonecrosis (ON) secondary to sickle cell disease (SCD) often progresses to femoral head collapse, requiring total hip arthroplasty (THA). However, this treatment has a limited durability and patients with SCD have higher rates of complications, requiring multiple revision operations. Identifying risk factors linked to ON in SCD can facilitate earlier precollapse diagnosis and surgical treatment aimed at preservation of the native hip joint.

Methods—Fifty-nine (59) children treated at our institution between January 2001 and April 2012 with SCD and ON, as diagnosed by magnetic resonance imaging (MRI) or radiographic imaging (XR), were compared to age- and sickle cell phenotype-matched (SS, SC, S β^0 , S β^+) controls with no evidence of ON. Two sided t-tests assuming unequal variances determined statistically risk factors and threshold values were assigned to calculate odds ratios.

Results—Systolic blood pressure ($p=1.2\times 10^{-4}$, OR=3.68), diastolic blood pressure ($p=0.0084$, OR=1.41), weight in the SCD-SS population ($p=0.04$, OR = 1.85), and hemoglobin (Hb) in the SCD-SS population ($p=0.036$, OR=2.56) were elevated in cases. Curiously, dividing the Hb by the hematocrit (HCT) to serve as a clinical proxy for the mean corpuscular Hb concentration (MCHC), produced an excellent predictor of ON ($p=2.06\times 10^{-6}$, OR=5.17), that was especially pronounced in the SCD-SS subpopulation ($p=2.28\times 10^{-7}$, OR = 8.65). Among children with SCD, the overall prevalence of ON was 9% (59/658) and the phenotype with the highest prevalence of ON was SBeta0 thalassemia with an ON prevalence of 11.1%. There was no observed correlation between ON and height, body mass index, cholesterol, mean corpuscular volume, HCT, or glucocorticoid use.

Conclusions—This data supports a novel clinical marker, the MCHC proxy, as the strongest predictor of ON in children with SCD. High-risk children should receive hip MRIs to diagnose early ON and facilitate interventions focused on hip preservation, forestalling, or possibly preventing, the need for THA.

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Conflicts of Interest:

The authors have no other declared conflicts of interest.

Level of Evidence—Level III – Retrospective case-control study.**Introduction**

Osteonecrosis (ON) of the femoral head in sickle cell disease (SCD) has an insidious onset, and in the majority of patients progresses to femoral head collapse with rapid destruction of the hip joint [1-3]. A diverse array of joint-preserving treatments, ranging from core decompression to osteotomies, as well as vascularized and non-vascularized bone grafting, have been described [4-9]. However, the success rates of these techniques hinge upon intervention in early stage disease. Whereas, end-stage disease, characterized by extensive femoral head collapse, often requires total hip arthroplasty (THA) to relieve intractable pain and restore joint function [1, 3]. Since ON in SCD frequently occurs in children and young adults, it becomes imperative to diagnose ON early in an attempt to preserve the native joint.

Avascular necrosis (AVN) is a specific form of osteonecrosis driven by bone ischemia disrupting healthy bone remodeling, and is presumed to be the principle driver of ON in SCD [10, 11]. Unlike ON from other etiologies, cases seen in the context of SCD occur earlier in life and present with later stage disease [10, 12]. In fact, SCD is the most common cause of ON of the femoral head among children, observed in children as young as five years old with an increasing incidence throughout childhood and adolescence, peaking in early adulthood particularly in homozygous hemoglobin (Hb) SS disease [13]. SCD due to double heterozygous hemoglobinopathies (hemoglobin SC, hemoglobin S β^+ thalassemia, hemoglobin S β^0 thalassemia) also develop ON although it typically presents later in life in hemoglobin SC and hemoglobin S β^+ thalassemia [2, 13-16]. Furthermore, painful vaso-occlusive events (VOEs) mask early ON from both the patient and the clinician contributing to advanced stage disease presentation. Finally, patients with SCD have significantly higher THA failure and revision rates than all other causes [17, 18].

This combination of an early onset, advanced stage disease presentation, poor THA outcomes, and unclear ON risk factors especially in the pediatric population [13, 16], highlights the need for clinical predictors of ON in SCD.

The purpose of this study is to identify ON risk factors in children with SCD to promote targeted screening and earlier detection of precollapse disease, facilitating the use of treatment strategies directed at hip preservation rather than replacement. Additionally, ON risk factors have implications on the use of hydroxyurea, a medical therapy that stimulates fetal hemoglobin (HbF) production and has been shown to reduce the incidence of ON and VOEs in SCD [19, 20].

Materials & Methods

This protocol was approved by the Children's Hospital of Philadelphia Research Institute Committee for the Protection of Human Subjects.

Study Design & Procedures

Retrospective chart analysis evaluating fifty-nine (59) children with SCD (42 SS, 12 SC, 3 S β^+ thalassemia, 2S β^0 thalassemia) and ON as diagnosed with magnetic resonance imaging (MRI) or x-ray (XR) were compared to age- and sickle cell phenotype matched controls with no evidence of osteonecrosis. Children who were treated at our institution between January 2001 and April 2012, who were between 0 and 21 years old with an ICD9 code of AVN (344.70) of the femoral head and who also had comorbid sickle cell disease, were included as cases. Controls were chosen at random after matching age and sickle cell phenotype, among SCD patients at our institution who showed no evidence of ON by imaging or symptoms.

Variables Evaluated

Based on the current understanding of the pathogenesis of osteonecrosis, the following parameters were evaluated between cases and controls: body mass index (BMI), blood pressure, cholesterol, fetal hemoglobin, gender, glucocorticoid use, height, hematocrit (HCT), hemoglobin (Hb), hemoglobin to hematocrit ratio (Hb/HCT), hydroxyurea use, mean corpuscular volume (MCV), international normalized ratio (INR), triglycerides, and weight.

Retrieving Chart Data & Selecting Controls

In cases, the most recent lab values within the electronic medical record preceding the initial ON diagnosis were the values used in the statistical analysis. In controls, the most recent lab values were recorded. Of note, the age at diagnosis of ON in cases was the age used for matching with controls.

Statistical Analysis

The above variables were analyzed using two sided t-tests assuming unequal variances. Subset analysis of each putative risk factor was conducted for each of the SCD subtypes. Clinical factors found to be statistically significant were assigned intermediate threshold values to best dichotomize cases and controls into distinct groups to calculate odds ratios, since both threshold values and odds ratios are clinically useful. Threshold values were: 115mmHg for systolic blood pressure, 63mmHg for diastolic blood pressure, 52kg for weight, 0.33 for Hb/HCT ratio, and 9.0g/dL for Hb.

Results

Fifty-nine cases were found as described above and retrospectively compared to age and sickle cell phenotype matched controls across a variety of clinical variables. Baseline characteristics were broadly similar between cases and controls (Table 1). All cases had an MRI detailing ON of the femoral head except two, who had extensive Ficat stage IV disease [21] evident by XR and underwent THA (Table 2). Among controls, twelve had hip MRIs with no evidence of ON, twenty-six had no MRIs performed but normal hip XRs, while twenty-one had no imaging of the hips but were asymptomatic without hip or groin pain or gait abnormalities.

Primary Outcome - Risk Factor Assessment

Elevated blood pressure, Hb/HCT ratio, and increased hydroxyurea use were found in cases compared to controls (Table 3). Meanwhile, there was no statistically significant correlation between ON and other evaluated variables.

Subgroup analysis was performed on the SS, SC, S β^+ thalassemia, and S β^0 thalassemia populations to potentially identify specific SCD-phenotype risk factors. Within the Hb-SS subgroup, the elevated Hb/HCT ratio, Hb, systolic blood pressure, and weight were found to be positively associated with ON of the femoral head (Table 4). Diastolic blood pressure, within the Hb-SC subgroup, was found to be elevated in cases with a mean of 67.5mmHg +/-8 vs. 57.8mmHg +/-9 in controls ($p=0.038$). Additional subgroup analysis failed to yield statistical significance in any of the other examined variables.

Threshold values were applied to statistically significant clinical markers, stratifying cases and controls. The prevalence of these elevated risk factors amongst all cases and controls and specifically those with Hb-SS is shown in Figures 1 and 2 respectively.

Odds Ratios

Elevated Hb/HCT ratio above 0.33, produced an excellent predictor of ON of the femoral head (OR = 5.17) that was most pronounced in the Hb-SS population (OR = 8.65). Systolic blood pressure above 115mmHg proved to have the second strongest association with ON (OR = 3.68) and again, this trend was more prominent in the Hb-SS population (OR = 5.03) (Figure 3).

Secondary Outcome - Osteonecrosis Prevalence among SCD subgroups

Overall, of the 658 patients with SCD followed at our institution, 59 or 9.0% had diagnosed cases of ON with the highest prevalence among the Hb- S β^0 thalassemia subgroup (Table 5).

Discussion

In SCD, ON of the femoral head occurs early [13], presents with end stage disease [12], and has higher THA revision rates than all other causes (32% vs. 13%) and a high failure rate reaching 50% at 5.4 years postoperatively [12, 17, 18]. Furthermore, it is known that asymptomatic ON of the femoral head in SCD frequently progresses to femoral head collapse (73%) [1]. Leading some to recommend consideration of joint-preserving surgical intervention in asymptomatic ON regardless of lesion location or size [22, 23]. While others recommend hip-preserving surgical treatment for medium-sized, large, or laterally located asymptomatic lesions and watchful waiting in small, medially located, asymptomatic ON [1]. Among adults with SCD and symptomatic ON of the hip, progression to femoral head collapse is near inevitable with 87% of precollapse hips progressing to collapse within 5 years and a mean time to collapse of 42 and 30 months for Steinberg Stage I and II disease [24] respectively [3]. As a result, joint-preserving surgical intervention is recommended in early stage II disease, by Steinberg or Ficat classification, once ON changes are seen on XR. However, significant controversy remains regarding the optimal surgical treatment in precollapse disease [4, 6, 7, 9, 25, 26]. In summary, with likely progression to femoral head

collapse in symptomatic and asymptomatic disease, risk factors that can predict ON in children with SCD can target screening, identifying precollapse disease and allowing for interventions focused on hip preservation rather than replacement.

In this study, the prevalence of ON of the femoral head amongst various SCD phenotypes mirrors those seen in other pediatric populations[13]. While increased hemoglobin levels have been associated with ON in SCD [16], and our study found a similar trend in the Hb-SS subgroup (OR=2.56), it was the Hb/HCT ratio, simplified to a proxy of the MCHC (Figure 4), that serves as the most powerful predictor of femoral head ON in children with SCD. The baseline ON prevalence was 9.0% and thus the odds ratios approximate the relative risk. Therefore, an elevated Hb/HCT ratio above 0.33, which is equivalent to a MCHC above 33, has approximately a 5.17-fold increase in baseline ON risk, and an 8.65-fold increase in the Hb-SS phenotype. The pathophysiology behind this ratio has not been previously described. It may relate the HbS concentration within the red blood cell (RBC) with certain rheologic features of the blood and circulatory vessels known to affect polymerization and RBC sickling rates [27, 28]. Nonetheless, this MCHC proxy describes the propensity of the abnormal hemoglobin to polymerize, driving the RBC sickling and vaso-occlusion that underlie osteonecrosis in SCD.

Similarly, elevated systolic blood pressure can be utilized as a marker for ON risk (OR = 3.68, OR_{SS} = 5.03). Elevated blood pressure may contribute to ON by causing endothelial dysfunction and worsening hypercoagulability – a known contributor to bone ischemia in SCD [14, 29]. Alternatively, elevated blood pressures may simply share an association with a more severe phenotype of SCD with increased intravascular hemolysis, releasing nitric-oxide scavenging free Hb, leading to a vasoconstrictive and hypertensive environment [30]. Although diastolic blood pressure reached statistical significance, clinically the difference was minimal as 57% of cases and 48% of controls had diastolic blood pressures above 63mmHg. Increased weight (OR_{SS} = 1.85) adds physical stress to the joint, and fat emboli or bone marrow adipocyte hypertrophy may exacerbate bone ischemia as seen in ON due to glucocorticoid use and alcoholism[31]. Hypertriglyceridemia was seen in cases but due to a paucity of triglyceride levels recorded, this trend failed to reach statistical significance (p=0.14). In brief, systolic blood pressure was the second most useful clinical predictor of ON risk, and suggests a potential benefit of antihypertensive medications that warrants additional investigation.

No association between ON and gender, height, BMI, PT-INR, mean corpuscular volume, hematocrit, or glucocorticoid (GC) use was observed. The vast majority of GC use was inhaled corticosteroids for asthma management. The two instances of methylprednisolone use were in cases who developed ON of the femoral head. The conservative reservation of hydroxyurea for severe SCD with frequent pain crises as recommended by the National Institute of Health[32] is underscored by its use in 37.9% of cases with presumably more severe SCD, and only 20.7% of controls (p=0.049). This reservation leaves a large population that could benefit from hydroxyurea therapy, which has been shown to have protective effect against developing ON [20] and an ability to mitigate other manifestations of SCD [19]. With successful joint-preserving treatments in early-stage disease and a medical therapy that could be applied prophylactically in an at-risk population, the

utilization of the Hb/HCT ratio can shift the management of ON children with SCD toward preservation of the native joint.

Limitations

As a retrospective case-control study that was not blinded, there are several inherent limitations. Data retrieval and analysis algorithms were strictly designed to mitigate much of this bias. Additionally, the statistical power of the study was limited by the 59 cases of ON of the femoral head found in our population of children with SCD. This power was particularly limited with the specific phenotype analysis, making it difficult to draw conclusions about clinical risk factors for the Hb-SC, Hb-S β^+ thalassemia, and Hb-S β^0 thalassemia populations. Furthermore, older cases had limited data available in the electronic medical records as seen in Table 3. Another key limitation is the absence of imaging proving no evidence of ON among some controls. It is not currently standard practice to screen asymptomatic children with SCD with MRIs. Thus, when retrospectively analyzed, few children without symptoms suspicious of hip ON received an MRI, although the majority had received hip XRs, and the remainder had no imaging and were considered controls based on the absence of symptoms suspicious for ON. While MRI is the gold-standard for detecting ON from all causes [33, 34], in asymptomatic SCD others have found MRI had no advantage over XR as a screening tool for ON of the hip [35]. Our study, with 15% of cases found to have stage I disease, similarly defined by Steinberg [24] and Ficat [21] as an abnormal MRI and normal XR (Table 2), supports MRI as the best tool for diagnosis of ON of the hip among children with SCD. Furthermore, it is unclear how medical treatment, namely blood transfusions and intravenous hydration used in the setting of SCD pain crises, impacts the Hb/HCT ratio. Theoretically, hydration and transfusion would alter both the Hb and HCT terms similarly, leaving the ratio stable. This is supported empirically, as any slight fluctuations due to medical therapy did not compromise its close association with ON. Despite the above shortcomings, we believe a recommendation to use the Hb/HCT ratio to facilitate the diagnosis and management of early-stage ON can be made.

Conclusions & Recommendations

ON in SCD frequently progresses to femoral head collapse in asymptomatic [1] and symptomatic disease [3]. An elevation in the MCHC or the Hb/HCT ratio is a clear risk factor for ON of the femoral head in children with SCD and warrants a bilateral hip MRI and consideration of hydroxyurea therapy. Steinberg[24] stage I disease should be closely evaluated at 6 month intervals [22] and stage II and III disease should prompt consideration of surgical intervention focused on joint preservation, forestalling or preventing the need for THA.

Future Works

Future studies should analyze the effect of applying the elevated Hb/HCT ratio to dictate screening MRIs and subsequent intervention, in terms of prognostic utility, efficacy of early surgical treatment, and time to THA. Additional investigation of the Hb/HCT ratio in terms of other SCD complications such as cerebrovascular accidents and ON in other areas is also warranted.

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Figure 1. Prevalence of Elevated Risk Factors in Cases & Controls. Threshold values of 0.33, 115mmHg, and 63mmHg, were set for the hemoglobin to hematocrit ratio (Hb/HCT), systolic blood pressure, and diastolic blood pressure, respectively.

$$\frac{[\text{Hemoglobin}]}{\text{Hematocrit}} = \frac{\frac{\text{Hemoglobin}}{\text{Blood Volume}}}{\frac{\text{Packed Cell Volume}}{\text{Whole Blood Volume}}} = \frac{\text{Hemoglobin}}{\text{Packed Cell Volume}} \approx \frac{\text{Hemoglobin}}{\text{Red Blood Cell Volume}}$$

Figure 2.

Prevalence of Elevated Risk Factors in Hb-SS Cases & Controls. Threshold values of 0.33, 115mmHg, 52kg, and 9g/dL were set for the hemoglobin to hematocrit ratio (Hb/HCT), systolic blood pressure, weight, and hemoglobin (Hb), respectively.

Figure 3.

Osteonecrosis Risk Factors Odds Ratios and 95% Confidence Intervals. Middle marker represents the odds ratio. End markers enclose the 95% confidence interval. Middle marker size correlates with the effect size corresponding to the number of data points available for analysis of each variable. Hemoglobin to hematocrit ratio (Hb/HCT), systolic blood pressure, hemoglobin (Hb), weight, and diastolic blood pressure odds ratios are shown above. Note (SS) denotes the odds ratio for the listed clinical parameter within the Hb-SS phenotype.

Figure 4. Simplification of the hemoglobin to hematocrit ratio to the mean corpuscular hemoglobin concentration (MCHC), which is the hemoglobin/hematocrit ratio multiplied by 100.

Table 1

Baseline Characteristics of Cases & Controls

Characteristics	Cases (N=59)	Controls (N=59)
Male - no. (%)	29 (49.2%)	28 (47.5%)
Female - no. (%)	30 (50.8%)	31 (52.5%)
Age at Diagnosis of Osteonecrosis (cases) and at Presentation (controls) (Mean +/- SD)	13.8 +/- 4.0	13.9 +/- 3.9
Hb-SS Phenotype - no. (%)	43 (72.9%)	43 (72.9%)
Hb-SC Phenotype - no. (%)	8 (13.5%)	8 (13.5%)
Hb-SB+ Thalassemia Phenotype - no. (%)	3 (5.1%)	3 (5.1%)
Hb-SBO Thalassemia Phenotype - no. (%)	5 (8.5%)	5 (8.5%)

Table 2

Radiographic diagnosis of fifty-nine cases with osteonecrosis of the femoral head.

Imaging study Diagnosis	Number of Cases	Percentage of overall cases
MRI positive, XR positive	42	71.2%
MRI positive, XR normal	9	15.3%
MRI positive, XR not performed	6	10.2%
MRI not performed, XR positive	2	3.4%

Table 3

Risk Factor Analysis

Putative Risk Factor	Cases (N=59)	Controls (N=59)	P - Value
	Mean +/- 1 standard deviation (# data points)	Mean +/- 1 standard deviation (# data points)	Two tailed, assuming unequal variance
Height (m)	1.58 +/- 0.17 (49)	1.52 +/- 0.17 (59)	0.12
Weight (kg)	53.3 +/- 19 (49)	48.1 +/- 15 (59)	0.13
Body Mass Index (BMI)	20.8 +/- 5.0 (49)	20.2 +/- 3.9 (59)	0.45
International Normalized Ratio	1.18 +/- 0.14 (43)	1.18 +/- 0.10 (32)	0.99
Hemoglobin (g/dL)	9.59 +/- 1.5 (57)	9.27 +/- 1.6 (59)	0.28
Hematocrit (%)	28.1 +/- 4.0 (57)	28.3 +/- 4.4 (59)	0.78
Mean Corpuscular Volume (fL)	86.4 +/- 13 (57)	86.9 +/- 12 (59)	0.84
BP-Systolic (mmHg)	118 +/- 9.0 (52)	111 +/- 10 (58)	1.2×10^4
BP-Diastolic (mmHg)	65.8 +/- 9.2 (52)	61.3 +/- 6.5 (58)	8.4×10^3
Cholesterol (mg/dL)	124.7 +/- 16 (20)	129 +/- 42 (9)	0.77
Triglycerides (mg/dL)	111 +/- 71 (18)	82.3 +/- 28 (9)	0.14
Hemoglobin/Hematocrit Ratio	0.342 +/- 0.017 (57)	0.327 +/- 0.015 (59)	2.1×10^{-6}
Fetal Hemoglobin (%)	9.09 +/- 7.5 (53)	10.4 +/- 9.8 (56)	0.37
Hydroxyurea use (%)	37.5 (56)	20.7 (58)	0.049
Glucocorticoid use (%)	19.6 (56)	24.1 (58)	0.57

Table 4

Statistically Significant Risk Factor Analysis in the Hb-SS Population

Risk Factor	SS Cases (N = 43)	SS Controls (N= 43)	P - Value
	Mean +/- 1 standard deviation (# data points)	Mean +/- 1 standard deviation (# data points)	Two tailed, assuming unequal variance
Hemoglobin (g/dL)	9.32 +/- 1.5 (38)	8.72 +/- 1.6 (43)	0.036
Hemoglobin/Hematocrit Ratio	0.341 +/- 0.017 (38)	0.326 +/- 0.015 (43)	2.3×10^{-7}
BP - Systolic (mmHg)	117.6 +/- 9.2 (35)	110.1 +/- 10.4 (42)	0.0011
Weight	54.7 +/- 19 (35)	47.4 +/- 10 (43)	0.041

Table 5

Prevalence of ON among SCD Patients at the Children's Hospital of Philadelphia with the hemoglobin (Hb) – SS, Hb-SC, Hb-Sβ⁺ thalassemia, and Hb-Sβ^o thalassemia phenotypes.

Phenotype	Patients with ON (#)	Total Number of Patients (#)	AVN Prevalence (%)	Phenotype in total population (%)
Hb-SS	42	402	10.4%	61.1%
Hb-SC	12	181	6.6%	27.5%
Hb-Sβ ⁺	3	57	5.3%	8.7%
Hb-Sβ ^o	2	18	11.1%	2.7%
Total	59	658	9.0%	