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Original research

Hemoglobinopathy is Associated With Total Hip Arthroplasty Indication Even Beyond Sickle Cell Anemia

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ABSTRACT

Background: The extent to which hemoglobinopathies other than sickle anemia (HbSS) are associated with hip osteonecrosis is unknown. Sickle cell trait (HbS), hemoglobin SC (HbSC), and sickle/β-thalassemia (HbSβTh) may also predispose to osteonecrosis of the femoral head (ONFH). We sought to compare the distributions of indications for a total hip arthroplasty (THA) in patients with and without specific hemoglobinopathies.

Methods: PearlDiver, an administrative claims database, was used to identify 384,401 patients aged 18 years or older undergoing a THA not for fracture from 2010 to 2020, with patients grouped by diagnosis code (HbSS N = 210, HbSC N = 196, HbSβTh N = 129, HbS N = 356). β-Thalassemia minor (N = 142) acted as a negative control, and patients without hemoglobinopathy as a comparison group (N = 383,368). The proportion of patients with ONFH was compared to patients without it by hemoglobinopathy groups using chi-squared tests before and after matching on age, sex, Elixhauser Comorbidity Index, and tobacco use.

Results: The proportion of patients with ONFH as the indication for THA was higher among those with HbSS (59%, $P < .001$), HbSC (80%, $P < .001$), HbSβTh (77%, $P < .001$), and HbS (19%, $P < .001$) but not with β-thalassemia minor (9%, $P = .6$) than the proportion of patients without hemoglobinopathy (8%). After matching, the proportion of patients with ONFH remained higher among those with HbSS (59% vs 21%, $P < .001$), HbSC (80% vs 34%, $P < .001$), HbSβTh (77% vs 26%, $P < .001$), and HbS (19% vs 12%, $P < .001$).

Conclusions: Hemoglobinopathies beyond sickle cell anemia were strongly associated with having osteonecrosis as the indication for THA. Further research is needed to confirm whether this modifies THA outcomes.

Introduction

Red blood cells transport oxygen to tissues throughout the body. The oxygen-carrying structure within red blood cells, hemoglobin, consists of 4 polypeptide globin chains and 4 iron-containing heme groups. Each adult hemoglobin molecule contains 2 alpha and 2 beta polypeptide globin chains [1]. Various mutations in the globin chains exist and have likely persisted secondary to increased host protection from malaria [2–4]. These mutations lead to variations in the protein structure that can have other varying clinical significance.

The sickle cell mutation is an amino acid substitution of glutamic acid for valine which leads to hemoglobin polymerization and subsequent red blood cell sickling which can be more common under physiologic stress such as hypoxemia [5], acidosis, and dehydration [4–6]. Hemoglobin C mutation is a different amino acid substitution of the beta globin chain which promotes dehydration of the red blood cell [7]. β-Thalassemia mutations cause a reduction or absence of globin synthesis from the affected beta globin chains [8].

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Two hemoglobin S mutations result in sickle cell anemia (HbSS) [9], the most common form of sickle cell disease [4], while a single hemoglobin S mutation results in sickle cell trait (HbS). Clinical manifestations of sickle cell anemia include acute chest syndrome, sequestration crisis, stroke, aplastic crisis, infection, priapism, ophthalmologic complications, ulcers on extremities, pulmonary hypertension, renal complications, iron overload, and osteonecrosis of the femoral head (ONFH) [10]. While the sickle cell trait is not associated with the same severity of clinical manifestations, these patients are susceptible to crises and other complications when under physiologic stress [11].

The S mutation can also be seen along with the C mutation resulting in hemoglobin SC (HbSC) disease [11]. Furthermore, the S mutation can be seen along with a β-thalassemia mutation, resulting in HbSβTh [11]. The dehydration of hemoglobin associated with the C mutation in combination with the hemoglobin S mutation can promote sickling [12]. β-Thalassemia leads to reduced or absent protein production of the affected chain, which, in combination with a sickle mutation, can magnify the effects of sickling.

The association between HbSS and ONFH is well appreciated within the literature [13–16]. Sickled red blood cells are less able to conform to mechanical deformation within capillaries, frequently causing vascular obstruction and inflammation [4]; in the femur, vascular occlusion contributes to ONFH [4]. Some studies have examined sickle cell disease subtypes and ONFH; however, controlling for confounding has been limited [17]. In the general population, the most common indication for total hip arthroplasty (THA) is osteoarthritis [17]. Within the HbSS population, osteonecrosis is the predominant indication for a THA [18]. The extent to which hemoglobinopathies other than HbSS are associated with ONFH remains relatively unexplored. We sought to compare the distributions of indications for a THA in patients with and without specific hemoglobinopathies. We hypothesized that osteonecrosis would be a more common indication for patients with hemoglobinopathies than for patients without hemoglobinopathy when controlling for confounding factors.

Material and methods

A retrospective cohort analysis was conducted using PearlDiver's Health Insurance Portability and Accountability Act of 1996-compliant Mariner administrative claims database of all payer types from 2010 to October of 2020.

Patients older than 18 years with a American Medical Association Current Procedural Terminology code for THA (CPT-27,130) without an ICD-10 code for femur fracture within 1 year prior to the THA were included. Patients were then grouped using International Classification of Diseases, Tenth Revision diagnosis codes based on the presence of hemoglobinopathy (Appendix). β-Thalassemia (HbβTh) has no pathophysiologic link to sickling and was included as a negative control. Additionally, patients with HbS and HbβTh with a record of hydroxyurea use, despite hydroxyurea typically not being indicated for these conditions, were excluded to limit the impact of inaccurate ICD coding. Osteoarthritis and osteonecrosis were then defined using ICD-10 codes (Appendix).

In total, 384,893 patients were identified including 210 with a diagnosis HbSS, 196 with a diagnosis of HbSC, 129 with a diagnosis of HbSβTh, 356 with a diagnosis of HbS, and 142 with a diagnosis of HbβTh. The prevalence of osteoarthritis and osteonecrosis as the underlying indication for THA in these matched groups was then compared using chi-squared tests.

Patients in each hemoglobinopathy group were then matched to patients without hemoglobinopathy on age, gender, Elixhauser Comorbidity Index (ECI), and a diagnosis of tobacco use disorder. Race is not recorded for many of the patients in the PearlDiver database and could not be used for matching. The prevalence of osteoarthritis and osteonecrosis as the underlying indication for THA in these matched groups was then compared using chi-squared tests. For all analyses, an alpha threshold of 0.05 was used to define statistical significance, and no adjustment was made for multiple comparisons.

Results

Patients with hemoglobinopathy tended to be younger, more likely to smoke, and have a higher ECI (Table 1). Among the unmatched populations that underwent THA, the hemoglobinopathy-free, HbS, and HbβTh populations appeared older than the HbSS, HbSC, and HbSβTh populations. Tobacco use disorder was significantly associated with HbSS (10%, $P < .05$), HbSC (15%, $P < .001$), HbSβTh (18%, $P < .001$), and HbS (12%, $P < .001$) compared with no hemoglobinopathy (6%). Additionally, the average ECI scores when compared to the hemoglobinopathy-free population (3.8 ± 3.1)

Table 1
Demographic characteristics by hemoglobinopathy group.

Characteristic	Hemoglobinopathy group					
	Without	HbSS	HbSC	HbSβTh	HbS	HbβTh
	N = 383,368	N = 210	N = 196	N = 129	N = 356	N = 142
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Sex						
Female	213,802 (56)	119 (57)	124 (63)	67 (52)	241 (68)	89 (63)
Male	169,566 (44)	91 (43)	72 (37)	62 (48)	115 (32)	53 (37)
Age						
<20	99 (0.030)	6 (3)	8 (4)	7 (5)	0 (0)	0 (0)
20-29	1,333 (0.35)	27 (13)	50 (26)	38 (29)	5 (1)	1 (1)
30-39	5,068 (1.3)	35 (17)	50 (26)	31 (24)	19 (5)	2 (1)
40-49	23,231 (6.1)	39 (19)	34 (17)	23 (18)	46 (13)	9 (6)
50-59	82,505 (22)	42 (20)	29 (15)	19 (15)	142 (40)	39 (27)
60-69	128,006 (33)	38 (18)	18 (9)	10 (8)	89 (25)	55 (39)
70-79	132,543 (35)	22 (10)	6 (3)	1 (1)	49 (14)	32 (23)
≥80	10,583 (2.8)	1 (0)	1 (1)	0 (0)	6 (2)	4 (3)
Tobacco						
Yes	23,215 (6.1)	21 (10)	29 (15)	23 (18)	43 (12)	4 (3)
No	360,153 (94)	189 (90)	167 (85)	106 (82)	313 (88)	138 (97)
ECI						
Mean (SD)	3.8 (3.1)	4.9 (4.0)	5.3 (3.7)	5.3 (4.1)	5.5 (3.9)	4.2 (3.7)

were significantly greater in the HbSC (5.3 ± 3.7, $P < .05$), HbSβTh (5.3 ± 4.1, $P < .05$) and HbS (5.5 ± 3.9, $P < .05$) populations.

The proportion of patients with ONFH was higher among those with HbSC (80%, $P < .001$), HbSβTh (77%, $P < .001$), HbSS (59%, $P < .001$), and HbS (19%, $P < .001$) but not HbβTh (9%, $P = .6$) than the proportion of patients without hemoglobinopathy (8%) (Table 2). After matching and compared to patients without a hemoglobinopathy, the proportion of patients with ONFH remained higher among those with HbSC (80% vs 34%, $P < .001$), HbSβTh (77% vs 26%, $P < .001$), HbSS (59% vs 21%, $P < .001$), and HbS (19% vs 12%, $P < .001$) (Table 3).

Discussion

This retrospective review of a large administrative claims database found that even patients with hemoglobinopathies other than sickle cell anemia were still more likely to have ONFH as the indication for a THA than those without a hemoglobinopathy. This association persisted even after matching for known confounders.

These findings build off previous work describing the potential association of various sickle cell disease types with ONFH. In a large study examining ONFH in the sickle cell population, Milner et al. [18] suggested the prevalence of ONFH within all sickle cell disease populations to be nearly 10% although others cite significantly higher rates [14,19]. They reported the highest prevalence of ONFH was within their subgroup of HbSβ^0Th patients with a complete deletion of the nonsickle beta chain group, followed by the HbSS, HbSC, and those with partial deletion of the nonsickle beta chain (HbSβ^+Th) groups. Our study showed similar outcomes with the HbSC population associated with the highest proportion of ONFH as the underlying THA diagnosis, followed by the HbSβTh and HbSS populations. The patient cohort of the referenced study comprised emergency room and hospital discharges, which may have introduced detection bias for ONFH by excluding healthier patients not seen in this setting.

As anticipated, the β-thalassemia minor population that lacked a sickle cell mutation did not share this association. This hemoglobinopathy population served as a negative control as the pathophysiology of β-thalassemia alone does not promote hemoglobin polymerization and subsequent sickling and, thus, does not support the development of ONFH. This further supports the findings of the study as the presence of a rare hemoglobinopathy alone does not seem to increase rates of ONFH leading to a THA.

The pathophysiology of osteonecrosis secondary to the sickle cell disease involves vaso-occlusion from obstructing sickled cells, which leads to subsequent hypoperfusion and inflammation [14]. Intraoperative complications due to sickling are not insignificant and can pose a significant challenge during the THA. Patients with sickle cell diseases have a high prevalence of thin trabeculae and cortices in addition to medullary canal sclerosis, which is likely due to chronic hypoxia and inflammation [20]. These factors contribute to the high rates of intraoperative fracture and cortical perforation in these patient populations. Sickle cell disease is also associated with increased rates of postoperative THA complications, including increased length of stay, infection, periprosthetic fracture, and aseptic loosening [14,19]. Waters et al. [21] further examined the complications associated with THAs in the sickle cell trait population and discovered a significantly increased rate of periprosthetic joint infection and prosthetic loosening, as well as a significantly increased odds of postoperative cerebrovascular accident, anemia, renal failure, pneumonia, sepsis, deep vein thrombosis, pulmonary embolism, and respiratory failure.

Importantly, increased surgeon awareness of the various sickle cell disease subtypes, as well as the effects of the sickle cell disease and trait on the femur, might allow for modified THA protocols and decreased complication rates in these patient populations [22]. Fassihi et al. suggested the utilization of a multidisciplinary team for medical optimization in the perioperative period, including measures of hydration and a transfusion protocol with a hemoglobin goal nearing 11 g/dL, followed by careful postoperative monitoring [20]. As for the optimal intraoperative protocol, there is no clear consensus within the literature. While the risk of intraoperative femoral fracture is higher for uncemented femoral stems than for cemented ones [23], cementing presents the possible risk of thermal necrosis of the infarcted bone, and earlier studies showed poor results with cemented femoral implants in patients with sickle cell disease [24]. Although recommendations pertaining to cemented vs uncemented fixation remain unclear [23], current trends in the United States favor the use of cementless components [25].

Hernigou et al. [22] discuss a protocol for the sickle cell disease population including preoperative and postoperative antibiotics, the use of cement containing antibiotics, as well as strict intraoperative oxygenation and hydration control. Postoperative antibiotic therapy was continued for 3 days if intraoperative cultures were negative and for 1 month if the cultures or histologic examination was positive. These modifications led to lower rates of complications than other reported rates of THA complications in sickle cell disease patients within the literature. This article highlights the need for further investigation into an optimized protocol for the subtypes of sickle cell disease or sickle cell trait.

It is also important to interpret these results in light of potential social implications. In the United States, a majority of patients with sickle cell disease variants are of Black race [26]. Black patients have also been shown to present for THAs at a younger age in the United States than their White counterparts [27], with worse preoperative symptoms compared to non-Hispanics [28]. Several studies have also reported increased complication rates in Black Americans undergoing a THA [29]. Many of these studies have either not reported the indication [30] for THA or not specified the etiology for ONFH [31].

Table 2
Unmatched distribution of THA indication.

Group	THA indication		*P* value
	Osteoarthritis	ONFH	
	N (%)	N (%)	
Without	285,307 (74)	30,741 (8.0)	Ref
HbSS	67 (32)	124 (59)	<.001
HbSC	21 (11)	157 (80)	<.001
HbSβTh	15 (12)	99 (77)	<.001
HbS	234 (66)	69 (19)	<.001
HbβTh	105 (74)	13 (9.2)	.6

Table 3
Matched distribution of THA indication.

Group	THA indication		*P* value
	Osteoarthritis	ONFH	
	N (%)	N (%)	
Without[a]	116 (55)	44 (21)	Ref
HbSS	67 (32)	124 (59)	<.001
Without[a]	82 (42)	66 (34)	Ref
HbSC	21 (11)	157 (80)	<.001
Without[a]	69 (54)	33 (26)	Ref
HbSβTh	15 (12)	98 (77)	<.001
Without[a]	265 (74)	36 (10)	Ref
HbS	234 (66)	69 (19)	<.001
Without[a]	99 (70)	17 (12)	Ref
Hbβ	105 (74)	13 (9)	.4

[a] Matched to the hemoglobinopathy population below.

It is therefore important to consider the underlying indication when investigating associations between race and THA and to understand whether an underlying diagnosis of ONFH related to a hemoglobinopathy other than sickle cell anemia is associated with increased surgical complexity or postoperative complications. If future research shows such associations, surgeons can be better prepared when counseling patients preoperatively and better able to anticipate intraoperative or postoperative complications. Because Black patients in the United States have already been shown to have decreased access to orthopedic care [32], any association between hemoglobinopathy and increased complication risk after a THA should be presented in the context of an informed perioperative risk assessment and to avoid any potential to increase health disparities by denying care to an already underserved population.

This study had several limitations. First, not all subtypes of the sickle cell disease were included. The complete spectrum of sickle cell–related diseases includes rare variants such as sickle/α-thalassemia, which the current ICD coding system does not accurately reflect. With that said, these are very rare, and their inclusion within another group would not be expected to significantly bias these results. Second, coding errors are a concern and may be particularly relevant to the analysis of a complex set of diseases. To limit the potential for misclassification bias, inclusion and exclusion criteria were carefully applied, and hydroxyurea use was considered in grouping patients based on having a specific hemoglobinopathy. Third, race is not generally recorded in the PearlDiver database, which restricted matching by this variable. Further investigation may be warranted given the previously mentioned demographic associations within the United States. These limitations are balanced against the strengths of the study which included the use of an administrative claims database, which is one of the few sources with enough patient records to identify a moderate number of patients with less common hemoglobinopathies. This is a factor that has limited much of the prior work attempting to describe the association of these diseases other than sickle cell anemia with ONFH.

Conclusions

Hemoglobinopathies beyond sickle cell disease were strongly associated with having osteonecrosis as the indication for THA. Further research is needed to confirm this pathophysiologic association and to understand how this modifies THA outcomes within these populations.

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There was no source of external funding for this work.

Conflicts of interest

A. Cohen-Rosenblum receives financial or material support from Elsevier and the Journal of Bone and Joint Surgery; is in the editorial or governing board of *Arthroplasty Today* and *Journal of Arthroplasty*; and is a member of the American Association of Hip and Knee Surgeons (AAHKS) nominating committee, AAHKS Young Arthroplasty committee, and Ruth Jackson Orthopaedic Society education committee. S. T. Duncan is in the speakers' bureau of or gave paid presentations for Smith & Nephew, OrthAlign, and BoneSupport; is a paid consultant for Smith & Nephew, OrthAlign, and BoneSupport; has stock or stock options in MiCare and ROM-Tech; receives research support as a principal investigator from Smith & Nephew, Medtronic, BoneSupport, Stryker, and Zimmer/Biomet; is in the editorial or governing board of Journal of the American Academy of Orthopaedic Surgeons, Journal of Arthroplasty, *The Knee*, and *Journal of Hip Surgery*; and is a board member or committee member in American Acedmy of Orthopaedic Surgeons Board of Councilors. C. A. Jacobs receives research support as a principal investigator from Smith & Nephew and Flexion Therapeutics; is in the editorial or governing board of the *Video Journal of Sports Medicine*; and is a board member or committee member in Orthopaedic Research Society. D. C. Landy is in the editorial or governing board of *American Journal of Sports Medicine*. P. K. Sculco receives royalties from Lima Corporate; is in the speakers' bureau of or gave paid presentations for Zimmer Biomet and Lima Corporate; is a paid consultant for DePuy Synthes, Intellijoint Surgical, Lima Corporate, and Zimmer Biomet; has stock or stock options in Intellijoint Surgical; and receives research support as a principal investigator from Intellijoint Surgical and Zimmer Biomet. All other authors declare no potential conflicts of interest.

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Appendix
Selection criteria.

Population	Inclusion criteria	Exclusion criteria	
Osteonecrosis	ICD-9-D-73342		
	ICD-10-D-M87351		
	ICD-10-D-M87352		
	ICD-10-D-M87353		
	ICD-10-D-M87851		
	ICD-10-D-M87852		
	ICD-10-D-M87859		
Osteoarthritis	ICD-9-D-71500 - ICD-9-D-71599		
	ICD-10-D-M1911 - ICD-10-D-M1993		
HbSS	ICD-10-D-D5700	ICD-10-D-D560	ICD-10-D-D573
	ICD-10-D-D5701	ICD-10-D-D561	ICD-10-D-D5740
	ICD-10-D-D5702	ICD-10-D-D562	ICD-10-D-D57411
	ICD-10-D-D571	ICD-10-D-D563	ICD-10-D-D57412
		ICD-10-D-D565	ICD-10-D-D57419
		ICD-10-D-D569	ICD-10-D-D5780
		ICD-10-D-D5720	ICD-10-D-D57811
		ICD-10-D-D57211	ICD-10-D-D57812
		ICD-10-D-D57212	ICD-10-D-D57819
		ICD-10-D-D57219	
HbSC	ICD-10-D-D5720	ICD-10-D-D561	ICD-10-D-D5740
	ICD-10-D-D57211	ICD-10-D-D562	ICD-10-D-D57411
	ICD-10-D-D57212	ICD-10-D-D563	ICD-10-D-D57412
	ICD-10-D-D57219	ICD-10-D-D565	ICD-10-D-D57419
		ICD-10-D-D569	
HbSβTh	ICD-10-D-D5740	ICD-10-D-D560	
	ICD-10-D-D57411	ICD-10-D-D562	
	ICD-10-D-D57412	ICD-10-D-D565	
	ICD-10-D-D57419		
HbS	ICD-10-D-D573	ICD-10-D-D560	ICD-10-D-D57212
		ICD-10-D-D561	ICD-10-D-D57219
		ICD-10-D-D562	ICD-10-D-D5740
		ICD-10-D-D563	ICD-10-D-D57411
		ICD-10-D-D565	ICD-10-D-D57412
		ICD-10-D-D569	ICD-10-D-D57419
		ICD-10-D-D5700	ICD-10-D-D5780
		ICD-10-D-D5701	ICD-10-D-D57811
		ICD-10-D-D5702	ICD-10-D-D57812
		ICD-10-D-D571	ICD-10-D-D57819
		ICD-10-D-D5720	hydroxyurea use
		ICD-10-D-D57211	
HbβTh	ICD-10-D-D563	ICD-10-D-D560	ICD-10-D-D57219
		ICD-10-D-D561	ICD-10-D-D573
		ICD-10-D-D562	ICD-10-D-D5740
		ICD-10-D-D565	ICD-10-D-D57411
		ICD-10-D-D569	ICD-10-D-D57412
		ICD-10-D-D5700	ICD-10-D-D57419
		ICD-10-D-D5701	ICD-10-D-D5780
		ICD-10-D-D5702	ICD-10-D-D57811
		ICD-10-D-D571	ICD-10-D-D57812
		ICD-10-D-D5720	ICD-10-D-D57819
		ICD-10-D-D57211	Hydroxyurea use
		ICD-10-D-D57212	