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

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INTRODUCTION: Mutations in one or both globin genes can lead to protein alterations that affect red blood cells, including predisposition to sickling (HbS mutation), dehydration (HbC mutation), and decreased hemoglobin production (HbβTh or β-thalassemia mutation). Further, combinations of mutations can occur, leading to diseases including hemoglobin SC disease (HbSC) and sickle/β-thalassemia (HbSβTh). In sickle cell anemia, patients have two copies of the HbS mutation (HbSS), which can cause extensive red blood cell sickling, capillary obstruction, and subsequent osteonecrosis of the femoral head (ONFH). While the association between sickle cell anemia and ONFH has been clearly demonstrated in the literature, the extent to which other hemoglobin mutations and combinations thereof are associated with ONFH is unknown. The purpose of this study was to compare the distributions of indications for total hip arthroplasty (THA) in patients with and without specific hemoglobinopathies to assess the clinical significance of these potential associations.

METHODS: An administrative claims database (PearlDiver) was used to identify patients 18 years of age or older undergoing THA for a diagnosis other than fracture from 2010 to 2020. Hemoglobinopathies and THA indication were classified using diagnosis codes. β-thalassemia minor, where one gene carries the thalassemia mutation, was included as a negative control given the absence of a clear pathophysiologic link to sickling. The proportion of patients with ONFH was compared by hemoglobinopathy groups using chi-squared tests with a 95% confidence interval. To control for confounding, patients with hemoglobinopathy were matched on age, sex, Elixhauser Comorbidity Index (ECI), and tobacco use to patients without hemoglobinopathy, and associations were reassessed using the chi-squared test.

RESULTS:

The search identified 384,401 patients who underwent THA and either did not have hemoglobinopathy or had one of the hemoglobinopathies of interest, including 210 with a diagnosis HbSS, 196 with a diagnosis of HbSC, 129 with a diagnosis of, 356 with a diagnosis of HbS, and 142 with a diagnosis of HbβTh as defined by the selection criteria. Patients with hemoglobinopathy tended to be younger, more likely to smoke, and have a higher ECI. The proportion of patients with ONFH was higher for those with HbSS (59%, P<.001), HbSC (80%, P<.001), HbSβTh (77%, P<.001), and HbS (19%, P<.001) but not HbβTh (9%, P=.6) compared to patients without hemoglobinopathy (8%). After matching and compared to patients without a hemoglobinopathy, the proportion of patients with ONFH remained higher for 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).

DISCUSSION AND CONCLUSION: In this retrospective review, we found that hemoglobinopathies beyond sickle cell anemia were strongly associated with having ONFH as the indication for THA when compared to those without hemoglobinopathy. Interestingly, even the clinically mild HbS shared this association. These findings persisted even after adjusting for known confounders including age, sex, comorbidity index, and tobacco use. As expected, patients with HbβTh did not share this association. The effects of HbSS on perioperative and postoperative THA complications are well appreciated. Our findings add to this, providing evidence that other sub-types of sickle cell mutation containing hemoglobinopathies are associated with ONFH as THA indication, and thus might also increase the surgical risks within these patient populations. Further research is needed to confirm the pathophysiologic association and to understand if this modifies THA outcomes.

Table 2: Unmatched

	THA Indication		
Group	Osteoarthritis N (%)	ONFH N (%)	P value
Without	285307 (74)	30741 (8.0)	Ref
HbSS	67 (32)	124 (59)	<0.001
HbSC	21 (11)	157 (80)	<0.001
HbSβTh	15 (12)	99 (77)	<0.001
HbS	234 (66)	69 (19)	<0.001
HbβTh	105 (74)	13 (9.2)	0.6

Table 3: Matched

	THA Indication		
Group	Osteoarthritis N (%)	ONFH N (%)	P-value
Without*	116 (55)	44 (21)	Ref
HbSS	67 (32)	124 (59)	< 0.001
Without *	82 (42)	66 (34)	Ref
HbSC	21 (11)	157(80)	< 0.001
Without*	69 (54)	33 (26)	Ref
HbSβTh	15 (12)	98 (77)	< 0.001
Without*	265 (74)	36(10)	Ref
HbS	234 (66)	69 (19)	< 0.001
Without*	99 (70)	17 (12)	Ref
Hbβ	105 (74)	13 (9)	0.4

* matched to hemoglobinopathy population below

Table 1: Demographic characteristics by hemoglobinopathy group

	Hemoglobinopathy group					
	Without N = 383,368	HbSS N = 210	HbSC N = 196	HbSβTh N = 129	HbS N = 356	HbβTh N = 142
Characteristic	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Sex						
Female	213802 (56)	119 (57)	124 (63)	67 (52)	241 (68)	89 (63)
Male	169566 (44)	91 (43)	72 (37)	62 (48)	115 (32)	53 (37)
Age						
<20	99 (0.030)	< 11	< 11	< 11	0 (0)	0 (0)
20-29	1333 (0.35)	27 (13)	50 (26)	38 (29)	< 11	< 11
30-39	5068 (1.3)	35 (17)	50 (26)	31 (24)	< 21	< 21
40-49	23231 (6.1)	39 (19)	34 (17)	23 (18)	46 (13)	< 21
50-59	82505 (22)	42 (20)	29 (15)	< 22	142 (40)	39 (27)
60-69	128006 (33)	38 (18)	< 24	< 21	89 (25)	55 (39)
70-79	132543 (35)	< 23	< 21	< 11	49 (14)	< 34
>=80	10583 (2.8)	< 11	< 11	0 (0)	< 11	< 11
Tobacco						
Yes	23215 (6.1)	21 (10)	29 (15)	23 (18)	43 (12)	4 (3)
No	360153 (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)

* Some data restricted to protect patient privacy.