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Prevalence of fractures among the Thalassemia syndromes in North America

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Abstract

Historically, fractures are cited as a frequent problem in patients with Thalassemia prior to optimization of transfusion and chelation regimens. The aim of this study was to determine the prevalence of fractures in a contemporary sample of North American patients with Thalassemia. The North American Thalassemia Clinical Research Network (TCRN) database registry was used to gather historical data on 702 patients with common alpha and beta-Thalassemia diagnoses including Thalassemia Major (TM), Intermedia (TI), E/Beta, homozygous alpha Thalassemia (AT), Hemoglobin H disease (HbH) and HbH with Constant Spring (HbH/CS), who consented to a medical record chart review. Bone mineral density (BMD) measurements by DXA were available for review in a subgroup of patients ($n = 312$).

The overall fracture prevalence among all Thalassemia syndromes was 12.1%, equally distributed between females (11.5%) and males (12.7%). Fractures occurred more frequently in TM (16.6%) and TI (12.2%) compared to E/Beta (7.4%) and alpha (2.3%). Prevalence increased with age (2.5% ages 0–10 years, 7.4% ages 11–19 years, 23.2% ages >20 years) and with use of sex hormone replacement therapy (SHRT) ($P < 0.01$). On average, BMD Z and T scores were 0.85 SD lower among patients with a history of fractures (mean Z/T score -2.78 vs. -1.93 , 95% CI for the difference -0.49 to -1.22 SD, $P = 0.02$). Presence of other endocrinopathies (i.e. hypothyroidism, hypoparathyroidism and diabetes mellitus), anthropometric parameters, heart disease or hepatitis C were not significant independent predictors of fractures.

These data indicate that fractures remain a frequent complication among the aging patients with both TM and TI beta-Thalassemia. However, the fracture prevalence has improved compared to published reports from the 1960s to 1970s. In addition, children with Thalassemia appear to have low fracture rates compared to the general population.

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Keywords

Thalassemia; Fractures; Low bone mass

Introduction

Historically homozygous beta-Thalassemia has been associated with severe osseous abnormalities, originally described by Cooley et. al. in 1925 [1]. Pathological fractures and premature epiphyseal fusion resulted in marked long bone deformities [2,3]. The pathogenesis of bone disease in Thalassemia has been ascribed to the underlying massive ineffective erythropoiesis, erythroid expansion of medullary bone with thinning of cortical bone, as well as metabolic and endocrine dysfunction secondary to transfusional iron load [4].

A high rate of fractures in Thalassemia patients was documented in the 1960s and 1970s when transfusion and chelation regimens were not optimized [5]. Over the past three decades, management of patients with Thalassemia has improved dramatically with hypertransfusion therapy, which has nearly normalized pre-transfusion hemoglobin levels, reduced the ineffective erythropoietic process and prevented bone deformities. Iron chelation using prolonged subcutaneous infusions of desferrioxamine (sc DFO) initiated in the mid-1970s has improved survival and diminished the endocrine complications of transfusional hemochromatosis [6,7].

Recent publications indicate that bone disease in Thalassemia in the form of low bone mass remains a frequent, debilitating and poorly understood problem, even among well-transfused and chelated pre-pubertal and adult patients [8–11]. The current frequency of fractures in beta-Thalassemia Major and in the various Thalassemia syndromes has not been well assessed. Data from the North American Thalassemia Clinical Research Network (TCRN) were analyzed to determine the current prevalence of fractures and the risk factors associated with increased bone fragility within the various Thalassemia syndromes.

Methods

The TCRN is an NIH-funded clinical research network in North America comprised of 5 core centers, 13 clinical satellites and a data coordinating center (Appendix 1). The TCRN developed a registry of demographic, clinical and treatment data of North American patients with beta, E/Beta, and alpha-Thalassemia (AT) syndromes. The registry was created to highlight and identify areas requiring clinical research and candidate patients who are potentially eligible for participation in multicenter clinical research protocols.

Registry data were assembled on all living patients of the TCRN by retrospective chart review and by patient self-report using a case report form covering demographic, genetic and anthropometric information, transfusion and chelation management, infectious, endocrine, cardiac, hepatic, iron-related and Deferoxamine (DFO)-related complications and data on history of fractures and bone mineral density.

Current and retrospective data for this report were entered once for each subject during the time period from May 2000 through December 2003. Ages reported are the ages at registry enrollment or at the time of particular events in the dataset. Institutional review boards approved the protocol at each site, and each subject or a parent or guardian gave informed written consent.

For the purpose of this report, beta-Thalassemia Major (TM) was defined as homozygous or compound heterozygous beta-Thalassemia requiring eight or more transfusions in the 12 months prior to enrolling in the Registry. Thalassemia Intermedia (TI) was defined as beta-Thalassemia receiving less than 8 units per year or not transfused (NT). Patients with E-Beta Thalassemia were divided into those with more or less than 8 units transfused annually or not transfused. Alpha-Thalassemia (AT) was also divided into three groups: Hemoglobin H (HbH), Hemoglobin H/Constant Spring (HbH/CS), which also includes non-deletional alpha-globin mutations and homozygous AT. Patients with successful engraftment of transplanted stem cells were excluded from analyses.

Fracture history was queried only for history of occurrence, not age of occurrence nor relationship to trauma. Measurement of bone mineral density (BMD) was performed by dual-energy X-ray absorptiometry (DXA) using Hologic (Hologic Inc. Bedford, MA) or Lunar (GE Lunar, Madison WI) scanners. BMD results from a small number of patients measured by different DXA models or by quantitative computed tomography were excluded from analysis. Records that did not report the type of DXA machine used were also excluded. Anteroposterior lumbar spine BMD measurements were expressed as *Z* scores for subjects up to the age of 20 years and as *T* scores for those 20 years old or older. *Z* and *T* scores were calculated from Hologic- and Lunar-specific norms.

Data validation

Over 80% of all registry forms have been reviewed for validation with sites targeting data of specific interest including diagnosis, genotyping, endocrinopathies, fracture history, hepatitis C and ferritin data. Independent source document verification was conducted for selected variables on approximately 20% of registry forms.

Statistical methods

Fracture prevalence was modeled by logistic regression (SAS version 9.1). BMD data were only available for a non-random sample of older patients, therefore separate models were considered with and without inclusion of BMD results as a covariate. Significance was accepted for $\alpha = 0.05$.

Results

At the end of 2003, the TCRN registry included 702 non-transplanted patients who had data on fracture history: 379 with TM, 58 with TI transfused less than 8 units annually, 40 TI not transfused (NT), 31 with E/Beta on regular transfusions, 41 E/Beta receiving fewer than 8 transfusions annually, 22 E/Beta not transfused, 80 with Hemoglobin H disease, 43 with Hemoglobin H/Constant Spring or other non-deletional alpha mutations and 8 with

homozygous AT. Basic demographics are presented in Table 1. Additional details are reported in Cunningham et al. (2004) [12].

A history of fractures was reported overall in 85 (12.1%) of the 702 patients in the TCRN registry, equally distributed between genders (11.5% in females versus 12.7% in males) (Table 2). Fractures occurred more frequently among patients with TM (16.6%) and TI (12.2%) compared to the other Thalassemia syndromes (7.4% in E/Beta and 2.3% in AT) (Table 3). However, among patients with E/Beta, the fracture prevalence was again higher at 12.9% among those who received more than 8 transfusions annually. Fracture prevalence was also highly dependent on age: 2.5% ages 0–10 years, 7.4% ages 11–19 years, 23.2% ages >20 years. However, the age distributions differ substantially among the various Thalassemia syndromes. Among the adult Thalassemia patients (age 20 years or older), fracture prevalence was 27.7% in TM, 22.9% in TI, 10.0% in E/Beta Thalassemias and 0% in AT (Table 3). No comparison among diagnosis, categorized as beta TM, TI, E/Beta and AT, was attempted in the young age groups because of the small reported number of fractures.

Age and diagnosis, categorized as beta TM, TI, E/Beta and AT, were significant independent predictors of fracture history in a model that included only demographic variables (age, diagnosis, gender and race). Fracture prevalence was higher among older subjects (odds ratio for a 5-year increase 1.45, 95% CI 1.30 to 1.62, $P < 0.001$) and lower among patients with AT relative to TM subjects (odds ratio 0.18, 95% CI 0.04 to 0.58, $P = 0.02$).

Fracture prevalence versus demographic, anthropometric, genetic and co-morbid conditions is given in Table 2. The use of sex hormone replacement therapy (SHRT) was a significant independent predictor of fracture risk (odds ratio of 2.33, 95% CI 1.25 to 4.33, $P < 0.01$). No difference was found with regard to androgen vs. estrogen replacement. Presence of other endocrinopathies including hypothyroidism, hypoparathyroidism and diabetes mellitus, anthropometric parameters, weight, height and body mass index (BMI), heart disease or hepatitis C were not significant independent predictors after controlling for age, diagnosis and SHRT. When the above analysis was also cross-referenced with duration of transfusions and years on chelation therapy (DFO), no correlation with fracture history was found.

BMD measurements by DXA utilizing either Hologic ($n = 174$) or Lunar ($n = 138$) scanners were performed in 312 patients in the registry (44%). This subgroup of patients with BMD data was significantly older and had greater co-morbidities and higher fracture prevalence. Limited BMD data for patients with alpha-Thalassemia precluded simultaneous estimation of diagnosis and Z/T score effects among all Thalassemia patients in the registry.

On average, BMD Z and T scores were 0.85 SD lower among patients with a history of fractures (mean Z/T score -2.78 vs. -1.93 SD, 95% CI for the difference -0.49 to -1.22 SD, $P = 0.02$). In a model that included demographics, anthropometrics, co-morbidities and BMD Z/T scores, the odds of reporting a history of fractures were higher among older patients (odds ratio for a 5-year increase 1.21, 95% CI 1.01 to 1.45, $P = 0.04$), among those who had ever used SHRT (odds ratio of 2.64, 95% CI 1.22 to 5.72, $P = 0.01$) and among

patients with lower Z/T scores (odds ratio for a 1-SD decrease = 1.46, 95% CI 1.05 to 2.03, $P = 0.02$). Fracture prevalence did not differ among TM, TI and E/Beta patients after controlling for age, SHRT and Z/T score.

Discussion

This report presents the current fracture prevalence in the largest series of Thalassemia patients identified globally to date. The TCRN results indicate a similarly high prevalence of fractures among patients with TM (16.6%) and TI (12.1%). This is expected as high rates of low bone mass are reported in both TM and TI (9). Lower fracture rates were observed in E/Beta (7.4%) and alpha-Thalassemia (2.3%). However, among patients with E/Beta, the fracture prevalence was again higher at 12.9% among those who received more than 8 transfusions annually. The lower frequency of fractures in non-transfused E/Beta and alpha-Thalassemia is most likely related to the moderate degree of hemolysis and low disease severity.

The results of this study confirm a decrease in fractures in beta-Thalassemia over the last decade. The first detailed study of bone deformities and fractures in patients with homozygous beta-Thalassemia was published in 1976 and reported fractures in 25 of 75 (33%) patients [5]. Subsequent reports in the 1980s found a high fracture frequency, which ranged from 30 to 50% [13,14]. Lower fracture rates, close to 15 to 19%, were reported in 1990s among transfusion-dependent beta-Thalassemia patients of Mediterranean and Middle Eastern origins [15,16]. Similar results were seen in a recent study from Singapore [17]. It was postulated that this decrease in fracture rates was the result of better transfusion and chelation regimens.

Epidemiological studies in the general population suggest that fracture incidence in the community is bimodal, with peaks in youth and elderly [18]. Before the age of 20, fractures are more frequent in men than women, involve the long bones and are the result of substantial trauma and, as such, usually reflect the lifestyle and sport activities of the community [19–23]. Accumulated fracture risk as high as 50% throughout growth has been reported [19]. Above the age of 40, fracture incidence rises again, in particular among women, and is primarily the result of decreased bone mass [24,25]. In contrast to the above, this study reports relatively low fracture prevalence below the age of 20 compared to the general population. This finding may be related to decreased physical activity due to illness in children with Thalassemia or reflects parental overprotection of the chronically ill child. In addition, our data indicate that the fracture prevalence in Thalassemia increases with age and among patients who have lower lumbar bone mass. This implies that fractures in Thalassemia are primarily the result of decreased bone mass. However, the presence of trauma in relationship to the fractures was not addressed in this analysis.

Treatment with SHRT, and by definition hypogonadism, was found to be a strong and independent predictor for fractures. While this is an expected finding [25,26], we have to acknowledge that the presence of hypogonadism is indirectly addressed in the registry. The age of diagnosis of hypogonadism in relationship to the fracture and the possibility of untreated hypogonadism both were not collected nor addressed, however, it is common

practice of all participating clinical centers in the Thalassemia network to treat hypogonadal patients with gonadal steroid replacement. An increased fracture frequency among subjects who used SHRT may reflect the failure of current gonadal steroid replacement regimens to restore bone mass to normal or may indicate increased disease severity and iron overload in those subjects who develop hypogonadism. It is of interest that neither the presence of additional endocrinopathies nor cardiac or liver diseases were independently associated with the prevalence of fractures in the analysis.

Limitations of this study include its retrospective design. Retrospective estimates of fractures sustained during childhood tend to be very low, presumably because of imperfect recall decades after the fracture event [24]. The types of bone fracture, relationship of fracture to specific trauma or occurrence of multiple fractures was not recorded in the registry. The age used for analysis is the age of enrollment in the registry and not the age that the fractures were sustained. Finally, BMD measurements were performed historically with two different technologies and without bone mineral content (BMC) data and volumetric adjustments of bone density to accommodate for size differences. Despite these limitations, the study reports on a large number of patients with various Thalassemia syndromes and confirms a high prevalence of fractures in the aging North American patient population with beta-Thalassemia. Furthermore, it identifies that fractures and bone disease remain unresolved problems in Thalassemia despite hypertransfusion regimens and improved chelation. The study points also to the need of further studies that will accurately evaluate the prevalence and risk factors that lead to bone disease in Thalassemia.

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Appendix A

The following institutions and researchers contributed to the Thalassemia Clinical Research Network Registry data reported in this paper:

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NHLBI Project Officer, Charles Peterson, MD

Data Coordinating Center: New England Research Institutes, Elizabeth Wright, PhD,
Principal Investigator

Table 1

Demographics

	Beta TM (<i>n</i> = 379)	Beta TI (<i>n</i> = 98)	E/Beta (<i>n</i> = 94)	Alpha (<i>n</i> = 131)
Age (years/range)	20.2 (1–51)	21.8 (0–58)	15.2 (0–48)	10.4 (0–62)
0 to 10 years (%)	23.2	35.7	37.2	63.4
11 to 19 years (%)	27.2	15.3	30.9	22.1
20+ years (%)	49.6	49.0	31.9	14.5
Gender (% male)	46.7	54.1	51.1	52.7
Race				
Caucasian (%)	61.5	63.3	3.2	4.6
Asian (%)	34.8	25.5	95.7	84.0
Other ^a (%)	3.7	11.2	1.1	11.5

^a‘Other race’ includes: African, African-American, mixed ethnic and unknown.

Table 2
Prevalence of bone fractures among various Thalassemia syndromes in the TCRN registry

Classification	n	Overall (%)			Beta-thal (%)			E/Beta (%)			Alpha-thal (%)		
		8/year n = 379	<8/year n = 58	NT n = 40	8/year n = 31	<8/year n = 41	NT n = 22	8/year n = 31	<8/year n = 41	NT n = 22	8/year n = 31	<8/year n = 41	NT n = 22
Overall	702	12.1	16.6	17.2	5.0	12.9	4.5	12.9	4.9	4.5	2.5	2.3	0.0
Gender													
Female	355	11.5	14.4	32.0	5.0	7.7	0.0	7.7	8.7	0.0	0.0	0.0	0.0
Male	347	12.7	19.2	6.1	5.0	16.7	8.3	16.7	0.0	8.3	5.1	4.0	0.0
BMD Z/T score													
-1.0 to ∞	64	4.7	5.4	0.0	0.0	0.0	33.3	0.0	0.0	33.3	0.0	0.0	-
-2.0 to -1.0	73	15.1	19.6	14.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
$-\infty$ to -2.0	175	27.4	29.0	38.9	20.0	0.0	0.0	0.0	20.0	0.0	0.0	0.0	-
Age (years)													
0 to 11	241	2.5	2.3	0.0	0.0	11.1	0.0	11.1	0.0	6.7	1.8	4.8	0.0
11 to 20	176	7.4	8.7	11.1	0.0	0.0	0.0	0.0	14.3	0.0	7.7	0.0	0.0
20 to 60	285	23.2	27.7	26.5	14.3	25.0	0.0	25.0	0.0	0.0	0.0	0.0	-
Race													
Asian	304	18.1	20.2	16.3	5.3	0.0	-	0.0	0.0	-	0.0	0.0	-
Caucasian	357	7.0	9.8	16.7	0.0	13.3	4.5	13.3	5.3	4.5	3.1	2.6	0.0
Other	41	12.2	21.4	33.3	12.5	-	-	-	0.0	-	0.0	0.0	-
Hypothyroid													
No	664	11.1	15.2	16.4	5.1	12.9	4.8	12.9	4.9	4.8	2.6	2.4	0.0
Yes	35	31.4	34.5	50.0	0.0	-	-	-	-	-	0.0	0.0	-
Hypoparathyroid													
No	688	11.6	15.8	17.5	5.0	12.9	4.8	12.9	4.9	4.8	2.5	2.3	0.0
Yes	12	41.7	41.7	-	-	-	-	-	-	-	-	-	-
Diabetic													
No	659	10.9	14.9	16.1	5.0	13.3	4.8	13.3	5.0	4.8	2.5	2.3	0.0
Yes	42	31.0	32.4	50.0	-	0.0	-	0.0	0.0	-	0.0	-	-
Sex HRT													
No	563	7.1	8.2	16.0	2.6	14.8	4.5	14.8	5.0	4.5	2.5	2.4	0.0
Yes	137	32.8	34.4	28.6	100.0	0.0	-	0.0	0.0	-	0.0	0.0	-
Endocrinopathies													
0	542	7.2	8.2	16.7	2.6	15.4	4.8	15.4	5.0	4.8	2.6	2.5	0.0
1	110	25.5	28.6	12.5	50.0	0.0	-	0.0	-	-	0.0	0.0	-
2	27	33.3	36.0	-	-	0.0	-	-	0.0	-	0.0	-	-
3	17	47.1	43.8	100.0	-	-	-	-	-	-	-	-	-
4	2	50.0	50.0	-	-	-	-	-	-	-	-	-	-
Hepatitis C													
Negative	483	12.4	14.4	18.2	9.5	15.4	6.7	15.4	6.5	6.7	6.5	0.0	0.0
Positive	101	21.8	25.0	50.0	0.0	0.0	-	0.0	0.0	-	-	0.0	-

Classification	n	Overall (%)	Beta-thal (%)		E/Beta (%)		Alpha-thal (%)				
			8/year n = 379	<8/year n = 58	NT n = 40	8/year n = 31	<8/year n = 41	NT n = 22	-/- α n = 80	-/ $\alpha^{CS}\alpha$ n = 43	-/- n = 8
Heart disease	No	10.3	14.0	16.1	5.1	10.0	5.1	4.5	2.5	2.4	0.0
	Yes	42.5	42.9	100.0	0.0	100.0	0.0	-	-	0.0	-
Height Z score	-1.0 to ∞	12.7	15.6	23.5	4.3	7.7	10.0	8.3	2.9	5.9	0.0
	-2.0 to -1.0	13.2	18.8	7.1	14.3	14.3	6.3	0.0	4.8	0.0	0.0
	$-\infty$ to -2.0	13.1	16.3	33.3	0.0	18.2	0.0	0.0	0.0	0.0	0.0
Weight Z score	-1.0 to ∞	12.3	17.4	8.3	8.3	15.4	11.8	0.0	1.9	4.5	0.0
	-2.0 to -1.0	11.8	13.8	33.3	0.0	10.0	0.0	16.7	5.9	0.0	0.0
	$-\infty$ to -2.0	11.7	16.9	33.3	0.0	12.5	0.0	0.0	0.0	0.0	0.0
BMI Z score	-1.0 to ∞	13.1	17.9	11.6	7.4	17.4	7.4	0.0	2.0	2.9	0.0
	-2.0 to -1.0	13.1	11.1	57.1	0.0	0.0	0.0	25.0	16.7	0.0	-
	$-\infty$ to -2.0	12.5	16.0	100.0	0.0	0.0	0.0	0.0	0.0	-	0.0
Beta genotype	$\beta^0\beta^0$	10.2	10.5	16.7	0.0	-	-	-	-	-	-
	$\beta^+\beta^0$	17.2	18.7	0.0	10.0	-	-	-	-	-	-
	$\beta^+\beta^+$	18.1	19.5	17.4	9.1	-	-	-	-	-	-
	$\beta^0\beta^E$	6.3	-	-	-	9.1	8.0	0.0	-	-	-
	$\beta^+\beta^E$	12.5	-	-	-	0.0	0.0	33.3	-	-	-
Alpha genotype	-/- α	3.1	-	-	-	-	-	-	3.1	-	-
	-/ $\alpha^{CS}\alpha$	2.8	-	-	-	-	-	-	-	2.8	-
	-/-	0.0	-	-	-	-	-	-	-	-	0.0

NT = non-transfused; HRT = hormone replacement therapy.

Table 3

Prevalence of bone fractures as reported in the TCRN registry

	Overall	0 to 11 years	11 to 20 years	20+ years
Beta TM	16.6% (63/379)	2.3% (2/88)	8.7% (9/103)	27.7% (52/188)
Beta TI	12.2% (12/98)	0.0% (0/35)	6.7% (1/15)	22.9% (11/48)
E/Beta	7.4% (7/94)	5.7% (2/35)	6.9% (2/29)	10.0% (3/30)
Alpha	2.3% (3/131)	2.4% (2/83)	3.4% (1/29)	0.0% (0/19)

Responses from chart review to the question “does the patient have a history of fractures?”.