Assessing Bone Quality and Fracture Risk by Trabecular Bone Score in Patients with Hemoglobinopathies

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Introduction

• Thalassemia (Thal) is a rare genetic disorder that prevents the body from producing a sufficient quantity of high quality blood. It is caused by a defect in erythroblasts to synthesize either the alpha or beta chain of adult hemoglobin.

• Sickle Cell Disease (SCD) is another genetic hemoglobinopathy caused by a single gene mutation in the hemoglobin molecule, resulting in abnormally shaped or "sickled" red blood cells.

• Both Thal and SCD are at high risk for low bone mass and osteoporosis for a variety of etiologies, though little is known about bone quality- and most importantly fracture.

• Trabecular bone score (TBS) is a new textural analysis software of lumbar spine bone density Dual Energy X-ray Absorptiometry (DXA) scans that reflects bone quality and microarchitecture.

• It is hypothesized that TBS in combination with a DXA scan may be more predictive of fracture in subjects with hemoglobinopathies than DXA alone.

Study Objectives

• To explore the relationship between bone mass (as assessed by DXA) and bone quality (as assessed by TBS software) in subjects with Thal and SCD in comparison to healthy controls.

• To assess the relationship between bone quality and clinical predictors that may be related such as age, transfusion status, liver iron concentration (LIC) , dietary intake, body mass index, and endocrinopathies.

Methods

• Study Design: A retrospective chart review.

• Subjects: >10 yrs and >40 kg with Thal or SCD who had a spine bone mineral density (BMD) DXA scan performed in the last five years. Data for our healthy control group were collected from subjects who previously completed research studies at BCHO; these were individuals without Thal or SCD.

• Analysis: DXA spine scans were re-analyzed using the TBS software (TBS iNsight, Medimaps v2.2, Mérignac, France). Some subjects had more than one scan performed during this 5 year period; these data were used to look at associations with TBS and change of TBS with time.

• TBS: Bone quality was categorized as:
Optimal: TBS ≥ 1.35
Subnormal: TBS= 1.34-1.20
Abnormal: TBS < 1.20

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Table 1: Subject Demographics at Baseline

	Thalassemia n=81	Sickle Cell Disease n=102	Healthy Controls n=68	p-value
Male/Female	36/45	41/61	12/56	0.001
%Male	44%	40%	18%	
African American	6	94	10	<0.001
Caucasian	20	0	31	
Asian or Hispanic	54	5	27	
Pediatric/Adult	13/68	52/50	13/55	<0.001
Age (years)	29.7 ± 11.1	23.8 ± 14.1	25.8 ± 8.2	0.002
BMI (kg/m²)	22.3 ± 3.6	23.1 ± 4.6	24.7 ± 5.9	0.01
Vit D 25OH (ng/mL)	29.3 ± 12.3	21.7 ± 8.4	27.1 ± 9.5	<0.001
Diet Calcium (mg/d)	724 ± 705	582 ± 490	692 ± 366	0.000
Calcium Supplement	44.4%	19.6%	.	0.001
Vit D Supplement	63.0%	46.1%	.	0.058
Vit D Deficiency	31.0%	42.6%	22.6%	NS
Hypogonadism	30.7%	1.0%	0%	<0.001
Hypothyroidism	14.1%	0.0%	0%	<0.001
Diabetes	9.0%	2.0%	0%	0.032
Transfusion Therapy	65.4%	23.5%	0%	<0.001
LIC (µg Fe/g wet wt.)	2303 ± 1823	3014 ± 2108	.	0.004
Hip BMD Z-score	-1.5 ± 1.3	-0.6 ± 1.1	-0.1 ± 0.9	<0.001
Spine BMD Z-Score	-2.1 ± 1.2	-1.0 ± 1.5	-0.1 ± 0.8	<0.001
Spine TBS	1.27 ± 0.12	1.31 ± 0.11	1.44 ± 0.10	<0.001

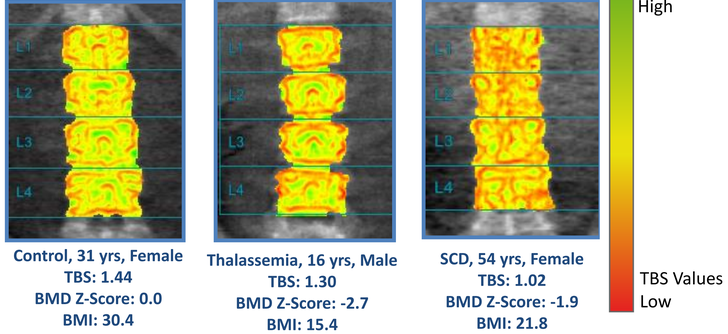
Vitamin D Deficiency: <20 ng/mL, BMI: Body Mass Index; LIC: liver iron concentration.

Table 2: Summary of Fracture Characteristics in Subjects with Thal, SCD and Healthy Controls

	Thalassemia	Sickle Cell Disease	Healthy Controls	p-value
Fracture History	22.4%	20.0%	32.1%	NS
Subjects with More than One Fracture, %	7%	2%	14%	NS
Location of Fracture, %				
Upper Extremity	33%	25%	22%	NS
Lower Extremity	22%	25%	22%	
Spine, Back, Pelvis	28%	30%	33%	
Other	0	30%	22%	
Cause of Fracture, %				
Fall	20%	23%	44%	0.16
MVA	27%	14%	0	
Fragility	***20%***	9%	0	
Other	7%	32%	0	
Recreational	27%	23%	56%	

No difference in prevalence or number of fractures, or surprisingly in location of fracture compared to controls. Though fragility fractures were more common in this young cohort of subjects with hemoglobinopathies (Ave Age of Thal + SCD Group= 27.7 years).

Figure 1: Optimal, Sub-Normal and Abnormal Bone Quality by Trabecular Bone Score (TBS) in Three Subjects with Varying Levels of BMD by DXA

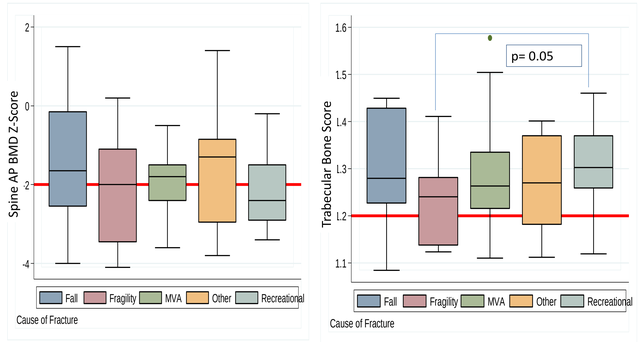


Control, 31 yrs, Female
TBS: 1.44
BMD Z-Score: 0.0
BMI: 30.4

Thalassemia, 16 yrs, Male
TBS: 1.30
BMD Z-Score: -2.7
BMI: 15.4

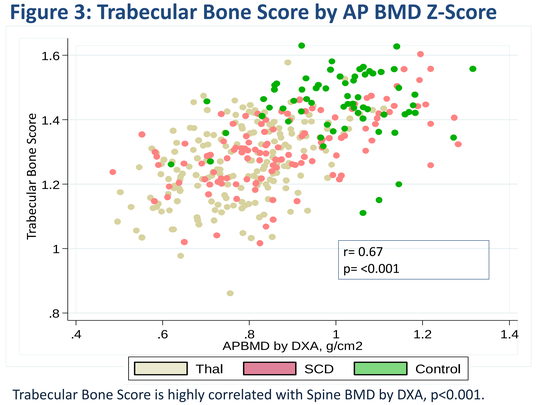
SCD, 54 yrs, Female
TBS: 1.02
BMD Z-Score: -1.9
BMI: 21.8

Figure 2a & 2b: Spine BMD Z-Score & TBS by Cause of Fracture In Subjects with Hemoglobinopathies



Spine BMD Z-score is not discriminatory with regard to type of fracture, e.g. fragility vs. Falls/Motor Vehicle Accident (p=NS). Whereas TBS is much lower (1.23) in subjects with fragility fractures, compared to those with recreational fractures, (1.30, p=0.05). Therefore, a combination of Spine Z-score + TBS may be valuable to predict low impact fractures.

Figure 3: Trabecular Bone Score by AP BMD Z-Score



Trabecular Bone Score is highly correlated with Spine BMD by DXA, p<0.001. Thal subjects have the lowest Spine BMD and TBS.

Table 3: Trabecular Bone Score by Subject Group

TBS	Thalassemia	Sickle Cell Disease	Controls	Total
Abnormal, #	57	20	3	80
Row%	**71%**	25%	4%	100%
Column%	28%	14%	5%	19%
Subnormal, #	93	72	5	170
Row%	55%	42%	3%	100%
Column%	45%	52%	8%	41%
Optimal, #	57	27	57	161
Row%	35%	29%	35%	100%
Column%	28%	34%	**88%**	40%
Total	207	139	65	
	50%	34%	16%	
	100%	100%	100%	

As expected, the majority of abnormal TBS Scans were in subjects with Thal (71%), while 88% of the controls had TBS scans in the optimal range, p<0.001.

Results

• On average, Thal adolescents and adults had greater deficits in Spine and Hip BMD Z-score, as compared to SCD and controls (Table 1, Fig 4).

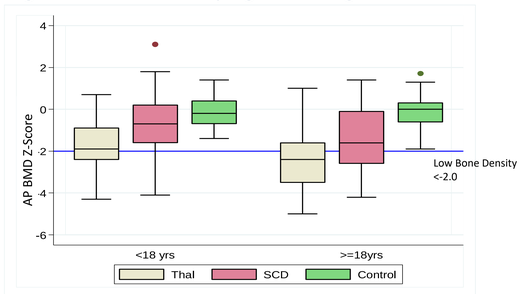
• Thal subjects had a higher prevalence of abnormal bone quality by TBS (28%) vs. 14% in SCD, 5% in control, (p<0.001).

• TBS was positively correlated with spine BMD Z-score, Hip Z-Score, Tx Therapy, and diagnosis. Negatively correlated with age, hypogonadism, and total dietary calcium (all p<0.05).

• After controlling for age, spine Z-score, hypogonadism and total calcium, Thal subjects have the poorest bone quality by TBS (r=0.28, p=0.001).

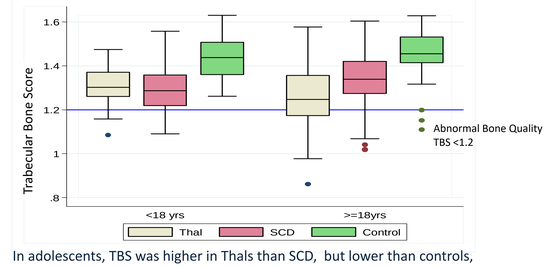
• Fragility fracture was common in Thal (20% of all fractures). Bone quality (TBS) was lower in those with fragility fractures than in those with other types of fractures (e.g. recreational, p=0.05).

Figure 4: AP Z-Score by Age and Diagnosis



Both in adolescents and adults, Spine BMD Z-Score was the lowest in Thals, followed in a stepwise pattern by SCD and controls.

Figure 5: Trabecular Bone Score by Age and Diagnosis



In adolescents, TBS was higher in Thals than SCD, but lower than controls, where as in adults, TBS was lowest in the Thal group. This is in contrast to the subjects observed with Spine BMD.

Conclusions

• These data support the relationship between reduced bone mass and bone quality in adolescent and adult subjects with hemoglobinopathies.
• Age is a predictor for TBS; older subjects with low bone mass are at a particular risk for fracture.
• Future research is needed to develop models that include BMD and TBS for prediction of absolute fracture risk and need for treatment of low bone mass in subjects with hemoglobinopathies.