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Infrequent fractures and resilient bone mineral density: bone health in patients with Fanconi anemia

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Running head: Fanconi anemia: fractures and bone density

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Fanconi anemia (FA) is the most common inherited bone marrow failure syndrome (IBMFS), characterized by a range of physical abnormalities, frequent bone marrow failure and cancer predisposition[1]. Endocrine complications in individuals with FA are common, and regular life-long follow-up with an endocrinologist is recommended [2]. Individuals with FA are at increased risk for decreased bone mineral density (BMD) secondary to factors including pubertal delay, poor growth [3,4], and hematopoietic stem cell transplant (HSCT)[5,6]. More individuals with FA are surviving into adulthood because of improved strategies for HSCT, along with established guidelines for screening for malignancy. Bone mineral density (BMD) is determined using dual-energy x-ray absorptiometry (DXA) scans and reported as a Z-score in pediatric patients[7]. Data evaluating BMD and fracture patterns in patients with FA are limited to either retrospective studies analyzing a dual energy x-ray absorptiometry (DXA) scan at a single timepoint or exclusively evaluating patients with FA who have previously undergone HSCT[5,6,8,9]. Our primary objectives were to characterize the incidence of fracture and evaluate BMD in a large cohort of patients with FA.

We conducted a retrospective cohort analysis of patients with FA treated at Cincinnati Children's Hospital Medical Centre (CCHMC) between January 2010 and December 2022. This study was approved by our Institutional Review Board. Patients were excluded if they did not have at least one DXA study available for analysis. Within the HSCT cohort, BMD data were compared using the first DXA post-HSCT, typically performed at the first annual post-HSCT visit. In the non-HSCT group, the first DXA ever was used to compare BMD across all patients. All DXA studies were sex-, age-, and

race-adjusted. Individual patient records were reviewed for clinical, demographic information and transplant-related characteristics if applicable.

Patient records were reviewed for evidence of fracture on radiographic imaging obtained at our institution or at an outside facility. The presence of vertebral compression fractures was determined based on radiographic evidence from thoracolumbar radiographs, computed tomography scans and magnetic resonance imaging. A fragility fracture was defined as a fracture occurring from minimal trauma, such as a fall from standing height[10]. Traumatic fractures were defined as those that occurred from excessive or significant force applied on bone.

The first DXA obtained for each patient was used to compare BMD across all patients. All DXA studies were sex-, age-, and race-adjusted[11]. All DXA scans were obtained for clinical screening purposes according to our standardized institutional protocol on a densitometer (Delphi/Discovery/Horizon; Hologic, Marlborough, MA) calibrated to a common manufacturer's standard. All scans were reviewed for image quality, positioning and artifacts. Available vitamin D levels (ng/mL) within one month of DXA scan completion were analyzed for each patient.

Data were analyzed using SAS®, version 9.4 (SAS Institute, Cary, NC). Due to skewed distributions or small numbers, continuous data were summarized as medians with interquartile ranges (IQR: 25^{th}-75^{th} percentiles) while categorical data were summarized as frequency counts and percentages. Generalized linear mixed models with random

effects (to account for multiple DXA scans longitudinally by the same subject) were used to analyze BMD Z-scores over time. A *p*-value <0.05 was considered statistically significant.

Table 1 describes the clinical characteristics of all patients with FA included in this cohort (n=77). Sixty-three (82%) patients received HSCT, and 14 patients (18%) were not treated with HSCT. The majority of patients were Caucasian (63/77, 82%). As expected, the greatest number of patients had mutations in the *FANCA* gene (34/77). Other *FANC* complementation group mutations are further summarized in Table 1. Further transplant characteristics and outcomes are summarized in Supplemental Table 1. We had vitamin D levels available for 71.4% (n=55) of all patients. The majority of patients with FA had a history of taking vitamin D supplementation (69/77, 89.6%) and 13.8% (7/77) had vitamin D levels that were either deficient or insufficient. At the time of the first DXA, 24.6% of patients with FA had a clinical or laboratory diagnosis of hypogonadism. Only one patient received bisphosphonates for the treatment of fragility fractures in this cohort.

DXA results and fracture patterns are summarized for all patients in Table 2. Fractures were identified in 13 patients (17%) in this cohort. Fractures were further subdivided into fragility or traumatic fractures. Fragility fractures comprised the minority of fractures observed in this group (n=3, 23%) with one fragility fracture occurring in a patient at 10.5 years old and the remaining two fragility fractures occurring in adults (21.6 years and 40.9 years). Sites of fragility fractures included the humerus, vertebral body and wrist. Vitamin D levels were known for two of these patients at the time of

fragility fracture diagnosis. Both patients had sufficient (>20 ng/mL) vitamin D levels. Only one patient had evidence of hypogonadism based on clinical exam findings and reproductive hormone testing at the time of the fragility fracture. Traumatic fractures made up the majority of fractures (n=10, 77%) and typically occurred during adolescent years (13.1 years, IQR 1.3, 23.5).

The median age at the first DXA scan was 10.3 years old (IQR 8.4,13.5). Median spine BMD Z-scores in all patients were within normal range (-0.42, IQR -1.29, 0.47). After adjusting for height, spine height-for-age BMD Z-score (HAZ) for all patients were still within normal range (0.75, IQR -0.28, 1.27). Only one patient (1.2%) had low (Z score <-2) HAZ spine BMD Z-scores in the entire cohort, who had vitamin D deficiency (vitamin D level 9 ng/mL) at the time of his DXA but no history of fractures.

Longitudinal DXA modelling for patients with multiple DXA scans available for analysis are shown in Figure 2 for HSCT and non-HSCT patients. In transplanted patients, there were 11 (17%) patients with DXA scans available for analysis at more than one timepoint. For the majority of these patients, BMD remained consistent and stable within the normal range (β=-0.02, p=0.49, Figure 1A). Ten untransplanted patients with FA had DXA scans available for analysis at more than one timepoint. We observed a similar trend where most patients had normal BMD at time of first DXA and these continued to remain stable over time (β=0.004, p=0.95, Figure 1B).

In this study, we investigated fracture incidence and BMD in a large cohort of patients with FA. In general, we found that HAZ adjusted lumbar spine BMD Z-scores fell within normal ranges for nearly all patients with FA regardless of transplantation status. This was an unexpected observation of our analysis, given the known skeletal abnormalities and endocrinopathies that can occur in patients with FA[12]. Shankar RK *et al* previously reported that adults with FA had significantly lower BMD Z-scores in the National Cancer Institute Inherited Bone Marrow Failure Syndrome Study cohort but HAZ adjusted BMD Z-scores did not differ in children with FA[8]. Our data indicate low BMD is infrequent, remains stable over time and standard monitoring should be employed.

Interestingly, the incidence of fractures for all patients with FA were less frequent than has been reported to occur in the general pediatric population[13] . In the general pediatric population, up to 40-50% of boys and 30-50% in girls suffer from at least one fracture throughout childhood[14], often due to sports or activity-related injuries[14]. Our lower incidence of fractures may in part be due to our center's standard practice of diligently monitoring vitamin D status and standardization of vitamin D supplementation. Moreover, parents may limit activity of chronically ill children.

Our data showed nearly 14% of patients had low vitamin D levels (deficient or insufficient) at the time of initial DXA scan in all patients. This is in contrast to the general pediatric population where vitamin D deficiency has been reported in 40-75% of children[15]. Our institution is focused on vitamin D repletion, and it is possible this has benefited bone strength. It is also important to mention that none of our patients had

chronic GVHD nor prolonged steroid treatment, both of which we have previously shown to be statistically significant risk factors for fragility fractures and low BMD at one-year post-transplant in children undergoing HSCT at large[5].

Our work has both strengths and limitations. The strengths include a relatively large number of patients with FA at a single institution and the length of follow-up we had for patients compared to prior studies. To our knowledge, this is the first comprehensive study to evaluate fracture incidence in patients with FA. The retrospective nature of the study is a limitation. Prospective studies will be key to better understanding longitudinal bone health outcomes in patients with FA.

Our data show that patients with FA had normal BMD regardless of transplantation status after adjusting the shorter stature of some patients. We also found that fractures were relatively rare in patients with FA, with fragility fractures making up a small proportion of these fractures.

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Table 1. Patient demographics and clinical characteristics of Fanconi anemia patients who completed HSCT

	All patients (n=77)
Sex, n (%)	
Male	40 (51.9)
Female	37 (48.1)
Race, n (%)	
Caucasian	63 (81.8)
African American	8 (10.5)
Asian	3 (3.9)
Hispanic	2 (2.5)
Mixed	1 (1.3)
*FANC c*omplementation group, n (%)	
FANCA	34 (44.1)
FANC B	2 (2.6)
FANC C	14 (18.2)
FANC D1/D2	2 (2.6)
FANC E	1 (1.3)
FANC G	4 (5.2)
FANC I	2 (2.6)
FANC J	3 (3.9)
FANC L	2 (2.6)
FANC P	1 (1.3)
Unknown	12 (15.6)
HSCT, n (%)	
Yes	63 (81.2)
No	14 (18.8)
Hypogonadism, n (%)	17/69 (24.6)
Vitamin D supplementation, n (%)	69 (89.6)
Vitamin D level (ng/mL)*	
Sufficient (≥20)	48 (88.9)
Insufficient (>10-<20)	4 (8.2)
Deficient (≤10)	3 (5.6)
Bisphosphonate, n (%)	1 (1.6)

HSCT: hematopoietic stem cell transplant

*Vitamin D levels measured within one month of DXA-scan are reported

Table 2. Fractures and bone mineral density in patients with Fanconi anemia

	All patients (n=77)
BONE MINERAL DENSITY DATA	
Height-for-age Z-score (HAZ), median (IQR)	-1.62 (-2.64, -0.76)
Age at first DXA (years), median (IQR)	10.3 (8.4, 13.5)
Spine BMDZ, median (IQR)	-0.42 (-1.29, 0.47)
HAZ adj Spine BMDZ, median (IQR)	0.75 (-0.28, 1.27)
Low HAZ adj Spine BMDZ, n (%)	1 (1.2)
FRACTURE DATA	
Any fracture, n (%)	13 (16.9%)
Age at first fracture (years), median (IQR)	12.8 (9.3, 14.2)
Any fragility fracture, n (%)	3 (23.1)
Site of fragility fracture, n (%) Humerus Vertebral body Wrist	 1 (33.3) 1 (33.3) 1 (33.3)
Age at first fragility fracture, years, median (IQR)	21.6 (10.5, 40.9)
Any traumatic fracture, n (%)	10 (76.9)
Age at first traumatic fracture, years, median (IQR)	13.1 (1.3, 23.5)

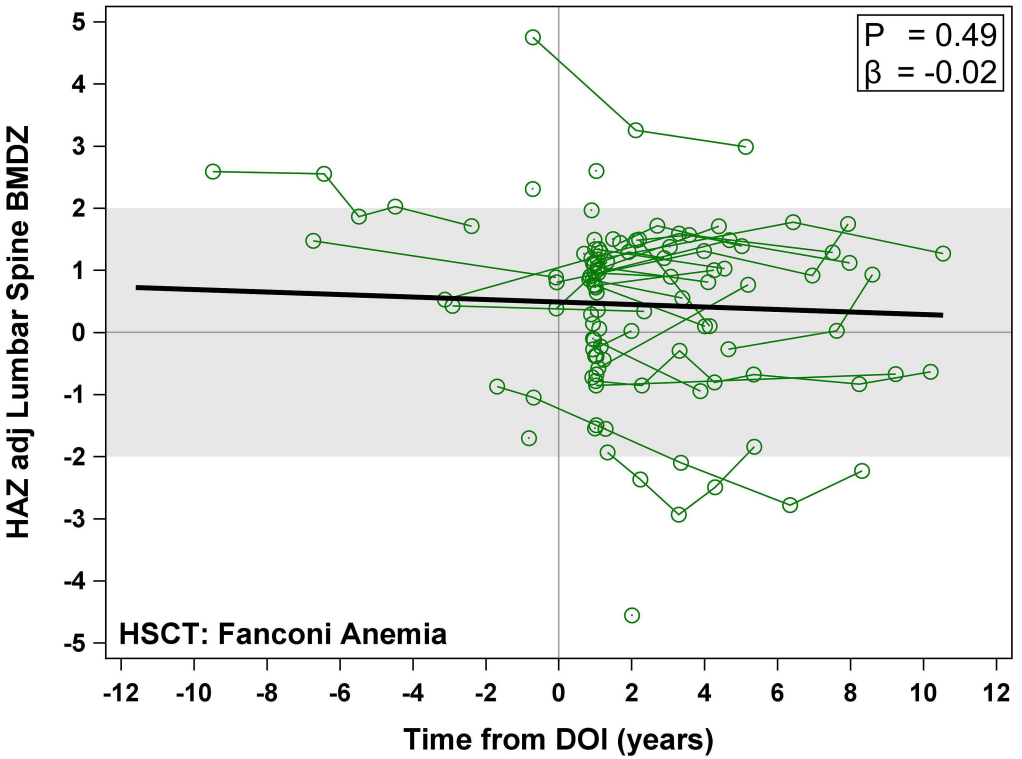
HAZ: Height-for-age Z-score; DXA: dual energy x-ray absorptiometry

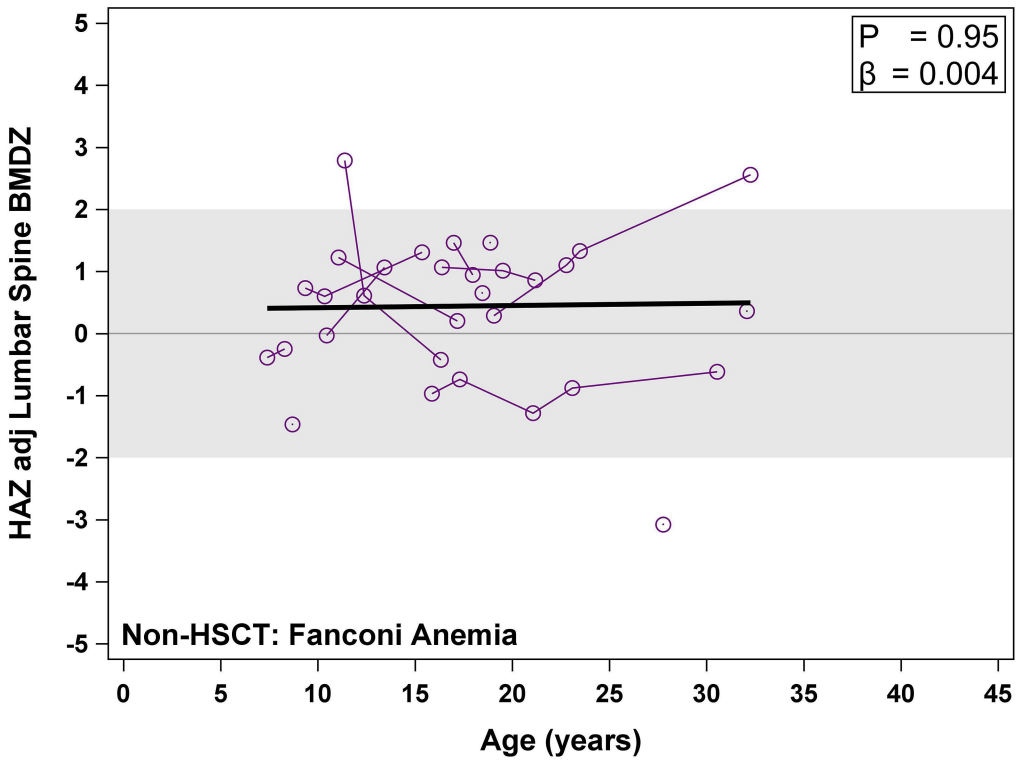
FIGURE LEGENDS:

Figure 1. Longitudinal changes in bone mineral density in HSCT and non-HSCT patients with Fanconi anemia

Shown are the longitudinal changes in lumbar spine height adjusted bone mineral density Z-scores (HAZ) in patients who received hematopoietic stem cell transplant (HSCT) with respect to time of HSCT (time 0). The grey zone spanning from bone mineral density (BMD) Z-scores between -2 and 2 represent normal BMD Z-scores. Each individual green line represents a single patient over time with each circle representing each time a DXA scan was completed. The overall linear regression analysis of all patients are represented by the bold black line. A) Regression analysis demonstrated a β coefficient of -0.02 over time in HSCT recipients ($p=0.49$). B) Regression analysis also demonstrated a stable β coefficient of 0.004 in non-HSCT recipients over time with age ($p=0.95$).

Figure 1


P = 0.49
β = -0.02
HAZ adj Lumbar Spine BMDZ
HSCT: Fanconi Anemia
Time from DOI (years)


P = 0.95
β = 0.004
HAZ adj Lumbar Spine BMDZ
Non-HSCT: Fanconi Anemia
Age (years)

Supplemental table 1. Transplant characteristics of patients with FA who received HSCT

	HSCT (n=63)
Age at first HSCT in years, median (IQR)	8.8 (6.3-10.6)
Donor type, n (%)	
Related	6 (10)
Unrelated	57 (90)
Degree of match, n (%)	
Fully matched	40 (63)
Mismatched	23 (37)
Stem cell source, n (%)	
Bone marrow	1 (1.6)
Peripheral blood stem cell	61 (97)
Cord	1 (1.6)
Conditioning regimen, n (%)	
Myeloablative	63 (100)
Reduced intensity	0
GVHD prophylaxis, n (%)	
CNI-based	24 (38)
T-cell depletion	39 (62)
Acute GVHD score at day 100, n (%)	
Grade I	2 (3.2)
Grade II	0

CNI: calcineurin inhibitor; GVHD: graft-vs-host-disease