American Journal of Hematology

WILEY

CORRESPONDENCE

Splenic Iron Overload Influence on Lumbar Spine BMD Reproducibility in β-Thalassemia

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Received: 25 May 2025 | **Revised:** 26 August 2025 | **Accepted:** 27 August 2025

Funding: The authors received no specific funding for this work.

Keywords: bone mineral density (BMD) | dual-energy X-ray absorptiometry (DXA) | splenic iron overload | β-thalassemia

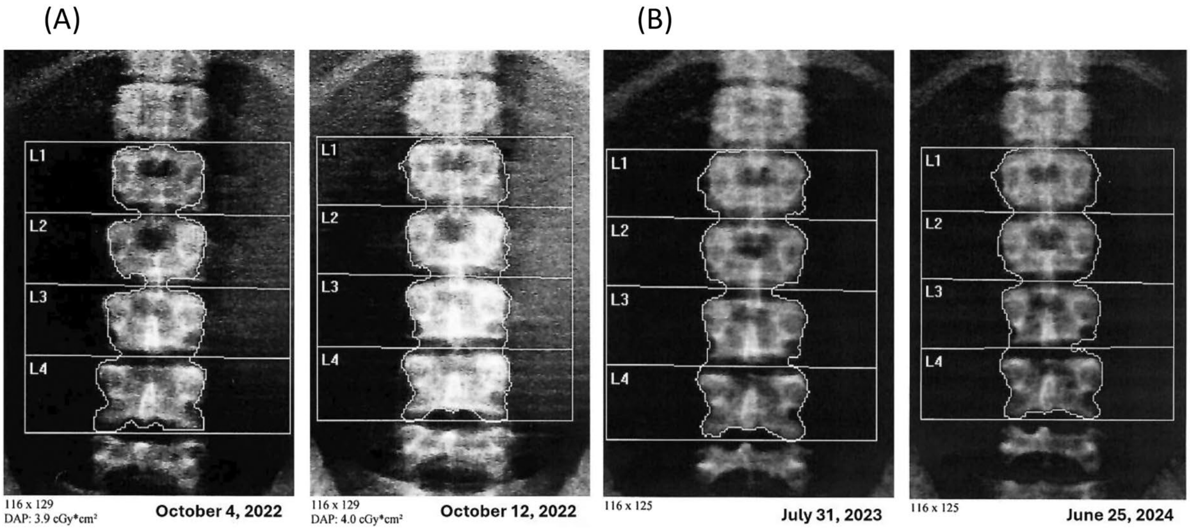
To the Editor,
Patients with β-thalassemia are at high risk for osteoporosis driven by a complex interplay of chronic anemia, iron overload, endocrine dysfunction, and marrow expansion [1]. Dual-energy X-ray absorptiometry (DXA) is the gold standard for measuring bone mineral density (BMD) in this population and guiding treatment decisions. However, the reliability of BMD assessments in thalassemia patients with heavy iron burden has been questioned, particularly at the lumbar spine (LS), where adjacent soft tissue artifacts from iron overload may compromise scan quality [2, 3].

We describe a unique case of transfusion-dependent thalassemia (TDT) with severe iron overload in whom wide variability in DXA measurements at the LS completely resolved following splenectomy. This observation prompted an investigation of BMD reproducibility in a cohort of thalassemia patients. Our aim was to assess the impact of iron overload on the precision of BMD measurements.

Our index case was a 26-year-old menstruating woman with a longstanding history of TDT. At the time of her initial DXA scan, she had ferritin levels > 6000 ng/mL and a liver iron concentration (LIC) of 13.45 mg/g. The DXA software failed to consistently detect bone edges at the LS, resulting in poor reproducibility, even on attempts to reanalyze the same scan on the same day. Repeated analyses of the same LS scan and of repeat LS scans over 2 months revealed extreme variability in BMD values (range: 0.643–1.096 g/cm^2), with a coefficient of variation (CV%) reaching 45.8%. A dense soft tissue artifact was noted lateral to the vertebrae, in the anatomical region of the spleen. By contrast, the detection of bone edges for the hip scan (femoral neck [FN] and total hip [THip]) and the results obtained were both highly reproducible. Abdominal MRI performed pre-splenectomy revealed a markedly enlarged spleen measuring 22 cm in craniocaudal dimension. The patient underwent splenectomy due to symptomatic hypersplenism, manifesting as anemia and severe thrombocytopenia refractory to medical management.

Following splenectomy, the artifact adjacent to the lumbar spine disappeared, and edge detection normalized. Serial LS scan analyses thereafter exhibited no variability, with same-day and different-day analyses yielding identical BMD values and a coefficient of variation of 0%. This direct before-and-after comparison suggests that splenic iron overload may interfere with LS BMD assessment by DXA (Figure 1).

To further explore this observation, we analyzed the reproducibility of BMD scan analyses at the LS in 21 adult β-thalassemia patients: 9 TDT and 12 non-transfusion dependent thalassemia (NTDT) scanned between January 2017 and July 2023 at our center. All were enrolled in thalassemia-related clinical trials and had undergone DXA as part of protocol-defined evaluations. Nineteen (90%) of the participants had undergone splenectomy, limiting our ability to perform subgroup analyses based



BMD (g/cm^2)	0.564	1.096	0.881	0.876
Z-score	-4.4	0.5	-1.5	-1.5

FIGURE 1 | (A) Pre-splenectomy LS DEXA scan with soft tissue artifact adjacent to the spleen; (B) Post-splenectomy LS scan showing artifact resolution and stable BMD. Please note the wide unexpected variability in BMD results in BMD and *Z*-scores in the first two scans obtained in 2022 pre-splenectomy, and the resolution of such variability post-splenectomy in 2023.

on splenectomy status. All had severe iron overload and were receiving deferasirox chelation therapy.

DXA scans were performed using the same densitometer as in the index case, a Hologic Discovery 4500 A QDR series, at the American University of Beirut Medical Center (AUBMC). This facility is accredited by the International Society of Densitometry. The ISCD certified technician reanalyzed each scan for the above cohort twice at the LS, FN, and THip on different days using the DEXA software. CV% was calculated for each skeletal site based on duplicate analyses.

Demographic data showed a mean age of 36 ± 7 years and a mean BMI of $20.6 \pm 1.9\,kg/m^2$. Average BMD values across the cohort were: LS $0.802 \pm 0.123\,g/cm^2$, FN $0.707 \pm 0.132\,g/cm^2$, and THip $0.778 \pm 0.151\,g/cm^2$. Fourteen participants (67%) had LS *Z*-scores below −2.0.

Wilcoxon signed-rank tests comparing duplicate analyses of BMD scans at each site showed a mean of 0.802 ± 0.123 and $0.799 \pm 0.125\,g/cm^2$ ($p = 0.62$) at the lumbar spine LS BMD; 0.707 ± 0.132 and $0.706 \pm 0.134\,g/cm^2$ ($p = 0.70$) on FN BMD; 0.778 ± 0.151 and $0.776 \pm 0.149\,g/cm^2$ ($p = 0.65$) at the lumbar spine THip BMD. These non-significant p values confirm the high reproducibility across scans.

The median CV% values for different-day duplicate analyses were 0.21% for LS, 0% for THip, and 0% for FN. These values fall well below ISCD-recommended thresholds of 1.9% (LS), 1.8% (THip), and 2.5% (FN), reinforcing the technical reliability of our DXA facility and protocols [4]. The 0% coefficient of variation we report here reflects the consistent and nearly identical bone edge detection by the DXA software on re-analysis of the same image in the 21 subjects as opposed to the index case, where edge detection was varying widely. In contrast, in vivo precision in daily QA programs including ours involves getting the patient off and on the table again, positioning the patient, and re-running the analyses using the second image acquired after repositioning, introducing the additional variability observed in clinical studies. Our yearly mean DXA reproducibility calculated across duplicate spine scans performed and analyzed on a daily basis is 0.62%.

Spearman correlation analysis found no significant association between BMD variability and markers of iron overload (ferritin, LIC, liver T2* MRI), suggesting that in splenectomized patients, systemic iron overload does not impair BMD precision. Quantitative imaging of splenic iron was not available for the two non-splenectomized patients; this is another limitation of our analysis.

The contrast between our index case and the study cohort highlights a potentially underrecognized source of DXA measurement variability: splenic iron overload. While several reports have noted altered BMD values in the setting of hepatic iron overload [2–5], none, to our knowledge, have directly assessed the impact of splenic iron on edge detection or performed serial imaging pre- and post-splenectomy. Our findings suggest that iron-laden splenic tissue adjacent to the lumbar vertebrae may disrupt bone edge detection and the soft tissue reference baseline values used in BMD calculations, leading to wide variability in bone density. Previous studies have yielded conflicting results. Allard et al. found hepatic iron elevated LS BMD values, possibly masking bone loss [2]. Conversely, Crabtree et al. observed underestimation of BMD due to overcorrection for soft tissue density in iron-loaded patients [5]. Ekbote et al. demonstrated improved LS BMD estimates in TDT patients after manually correcting for hepatic iron artifact [3]. However, none of these studies accounted for splenectomy status, a key variable in our analysis.

MRI-based quantification of splenic iron was not performed in our case. Therefore, while the anatomical location and resolution post-splenectomy strongly suggest iron overload as the cause of the artifact, alternative etiologies such as splenic calcifications or infarction cannot be completely excluded. Our study is also limited by its small sample size, and the fact that our cohort consisted almost exclusively of splenectomized patients; as a result, we were unable to perform a comparative analysis of CV% between splenectomized and non-splenectomized patients due to the small number of the latter ($n = 2$). Nonetheless, it is strengthened by its rigorous assessment of reproducibility of BMD measurements in our International Society of Densitometry (ISCD) accredited DXA facility, and the novel inclusion of serial pre- and post-splenectomy imaging data in the index case. We plan to specifically evaluate the effect of iron overload in the spleen on DXA reproducibility, by evaluating precision of BMD duplicate analyses at the LS and hip in subgroups of patients with and without splenectomy.

In conclusion, we propose that splenic iron overload can impair the reproducibility of lumbar spine BMD measurements by DEXA due to poor bone edge detection around vertebrae. Among splenectomized thalassemia patients, DEXA measurements at the LS, FN, and THip are highly reproducible, despite severe systemic iron overload. Technicians performing analyses on LS bone density scans in patients with β-thalassemia and iron overload, particularly those with intact spleens, and clinicians reporting them should pay attention to the presence of imaging artifacts and assess them for reproducibility of bone edge detection around the vertebrae. Such standardized protocols will enhance the diagnostic accuracy and the reliability of serial changes in BMD measurements in this population.

Acknowledgments

We thank the patients and families who participated in this study and our DXA department for their diligence and high quality assurance standards.

Ethics Statement

This study was approved by the Institutional Review Board (IRB) of the American University of Beirut Medical Center (AUBMC) under approval number BIO-2025-0003.

Consent

Informed consent was obtained from all participants. The protocol for duplicate scan analyses of BMD measurements was also approved by the IRB at the American University of Beirut.

Conflicts of Interest

J.K., A.M., F.K., S.E., N.C., M.R., M.C., and G.E.H.F report no conflicts of interest. A.T. reports consultancy and research support from Agios, Ionis, and BMS.

Data Availability Statement

The data used for this article is available upon reasonable request to the corresponding authors and subject to IRB approval.

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