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Splenectomy Exaggerates Bone Loss in a Thalassemia Mouse Model

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Background

- Osteoporosis and fragility fractures occur frequently in hemolytic disorders such as β-thalassemias [1-3].
- Splenectomy, a common surgical procedure which helps maintain hemoglobin levels, is shown to be strongly correlated with an increased risk of osteoporosis in thalassemic patients [4].
- The mechanism(s) for splenectomy-induced osteoporosis is still not clear, and no post-splenectomy β-thalassemia animal models exist.
- The **purpose** of this study is to characterize the effects of the splenectomy procedure on bone homeostasis in a thalassemic mouse model.

Materials & Methods

- **Animal model**: in this study, a heterozygous mouse model of β0-thalassemia (Hbbth3/+) is used. This model demonstrates moderate anemia and severe splenomegaly, which is comparable to the pathophysiology of patients with β-thalassemia intermedia [5].
- **Experimental design:** At 4 weeks of life, surgical splenectomy was performed on both thalassemic mice and WT mice. Bone geometry and bone histomorphometry were comprehensively analyzed at both 10 weeks and 10 months post-splenectomy and then compared with sham controls of both thalassemic and WT

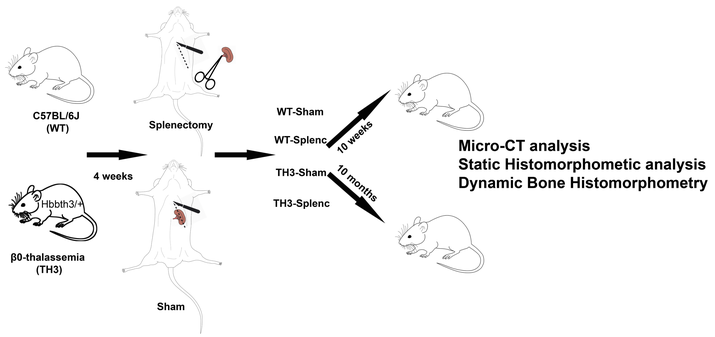

Figure 1. Schematic diagram of experiment.

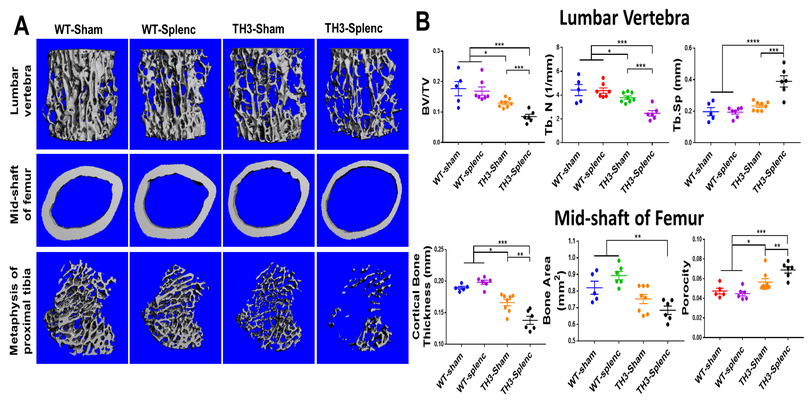

Figure 2. Micro-CT analysis. Splenectomy exacerbates the geometric parameters in both trabecular and cortical bones in thalassemic mice (TH3-splenc group) when compared with sham controls (TH3-sham group). However, splenectomy has no significant influence in WT controls (WT-splenc group vs WT-sham group). Data are expressed as mean ± SEM; *P<0.05, **P<0.01, ***P<0.001.

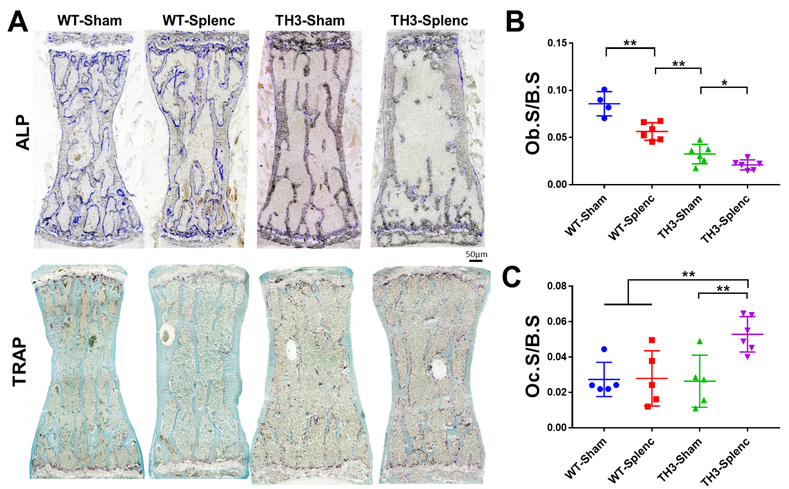

Figure 3. Static bone morphometric analyses. A. Representative images of Alkaline phosphatase (ALP) staining and Tartrate-resistant acid phosphatase (TRAP) staining on lumbar vertebra. **B.** Quantitative data of osteoblast surface (Ob.S/B.S). B.S, bone surface. **C**. Quantitative data of osteoclast surface (Oc.S/B.S). Data are expressed as mean ± SEM; *P<0.05, **P<0.01.

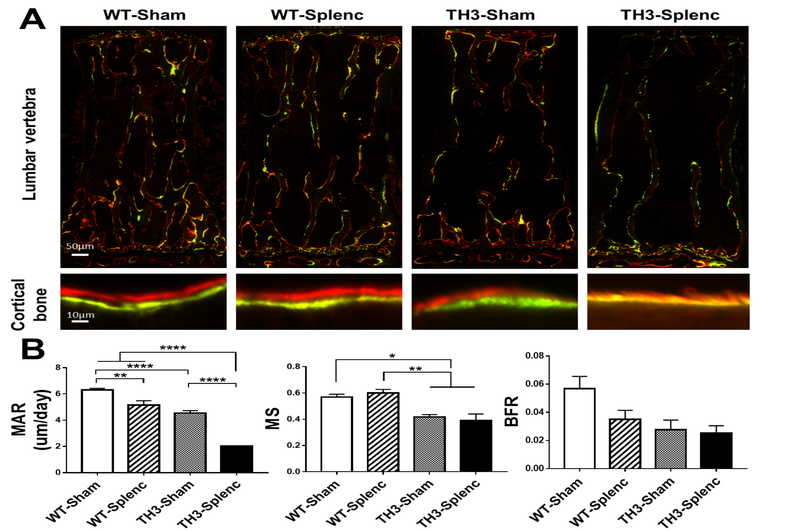

Figure 4. Dynamic bone morphometric analyses Thalassemic mice exhibit a significantly lower mineral apposition rate (MAR) and mineralizing surface (MS) when compared with WT controls. Further decreases in MAR and MS are observed in the splenectomized thalassemic group. Data are expressed as mean ± SEM; *P<0.05, **P<0.01, ****P<0.0001.

Conclusion

- This experiment is the first comprehensive assessment of bone quality and bone turnover in a thalassemic mouse model with and without the splenectomy procedure.
- Thalassemic mice demonstrate inferior bone quality. This reduced quality is associated with both decreased bone formation and increased bone resorption.
- Splenectomy exaggerates the bone loss observed in thalassemic mice but does not affect bone homeostasis in WT mice.
- The exaggerated bone loss observed in splenectomized thalassemic mice accurately represents the clinical observations in human patients.
- Further studies are needed to understand the underlying pathophysiology of splenectomy induced osteoporosis in thalassemia.

References

1. *Calcif Tissue Int. 2010;86(6):484-94;*
2. *J Orthop Res. 2015;33(9):1356-63;*
3. *Life Sci. 2017;173:55-61;*
4. *Cochrane Database Syst Rev. 2016(6):Cd010517;*
5. *Proc Natl Acad Sci U S A. 1995;92(25):11608-12*

Acknowledgements

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