Collagen X Biomarker Peaks During the Endochondral Phase of Fracture Repair with a Significant Temporal Correlation to Proteins within the Osteogenic Pathway

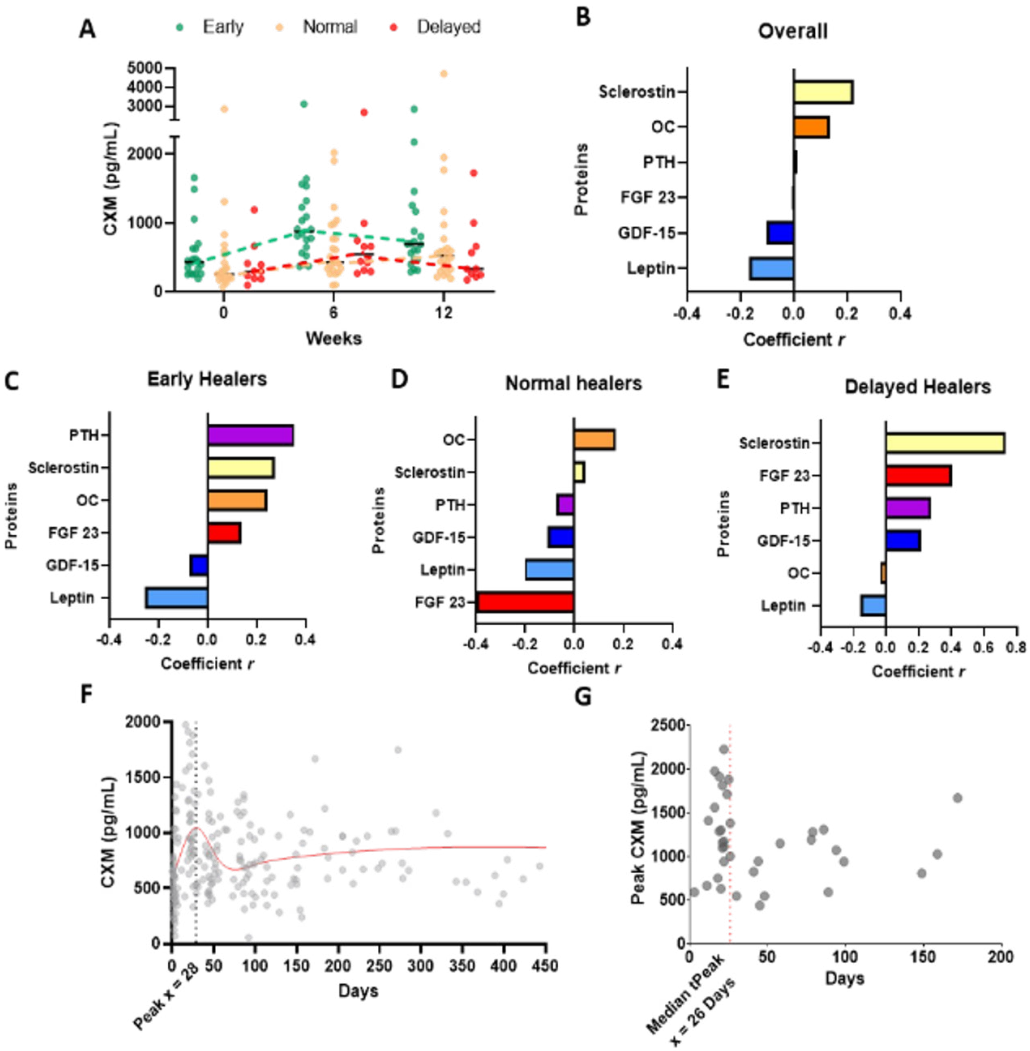
Zachary M. Working, MD*; Chelsea S. Bahney, PhD; Anna Laura Nelson, MS; Ryan Coghlan, BS; Kelsey M. O'Hara, BS; Molly E. Czachor, BS; Justin E. Hellwinkle, MD; Karalynn J. Lancaster, BS; Brian Johnstone, PhD; Sheila Sprague, PhD; Nathan N. O'Hara, PhD; Lauren Pierpoint, PhD; VitaShock Investigators; Gerard P. Slobogean, MD*

Purpose: There remains clinical interest in establishing biomarkers to predict fracture healing or identify patients at risk of nonunion. Bone turnover markers have been utilized in clinical management of osteoporosis but there remains limited evidence of efficacy in fracture repair. We recently reported on a degradation product of collagen X (CXM) as an investigational biomarker associated with endochondral remodeling of cartilage to bone and demonstrated that CXM correlates to bone healing both in preclinical fracture models and a clinical cohort of tibial plateau fractures. Here, we present data from 154 tibia/femur shaft fractures and investigate CXM correlation with 10 canonical bone biomarkers and fracture healing outcomes.

Methods: Acute tibia/fracture patients were enrolled in IRB-approved protocols across 3 sites. Blood, radiographs, and clinical notes were collected longitudinally throughout care; radiographs were collected and scored via mRUST (modified Radiographic Union Scale for Tibial Fractures) by blinded reviewers. Patients were grouped according to time to mRUST 12: early (<12 weeks), normal (13-26 weeks), delayed (>27 weeks). CXM assay, bone turnover markers, and a bone multiplex assay were completed on blood samples.

Results: We performed a secondary analysis of the VitaShock study (N = 102). Four patients with early healing exhibited a significant peak in CXM at 6 weeks relative to baseline values and this peak was higher than other healing groups (A, P = 0.016). A negative correlation was seen between leptin and CXM (P = 0.0415) and a positive correlation between sclerostin and CXM (P = 0.0057) (B). When segregated by healing, there was no correlation between CXM and any protein in early (C) or normal (D) healers, but parathyroid hormone levels had the next strongest positive correlation with early healing (C). In delayed healers, a positive correlation was seen between CXM and sclerostin (E: P<0.0001). Additionally, we prospectively enrolled fracture patients and collected blood at follow-up visits (N = 52). An XY scatter of CXM values in time showed the peak value tended to fall between 20 and 40 days (F), with median time to peak at 26 days (G).

Conclusion: Our study demonstrates that CXM may have value as a biomarker of fracture healing. In long bones, CXM peaks during the soft callus phase (~26 days). In the future, we hope to explore whether utilizing earlier detection of CXM increases the ability to predict healing progression.



The FDA has stated that it is the responsibility of the physician to determine the FDA clearance status of each drug or medical device they wish to use in clinical practice.