Hypercoagulability and Systemic Inflammation are Associated with Increased Venous Thromboembolism Risk in Orthopaedic Patients with Metastatic Bone Disease: A Pilot Study

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INTRODUCTION: With 600,0000 new cases of metastatic bone disease (MBD) annually in the United States, and up to 20% of these patients expected to develop pathologic fractures, MBD is a significant healthcare burden. Many patients with MBD will require orthopaedic surgical treatment, placing them at increased risk for potentially life-threatening venous thromboembolism (VTE). The pathophysiology of VTE is poorly understood in this high-risk patient group; however, there is increasing evidence supporting the interplay between hypercoagulability and inflammation during clot formation. Previous research has shown that thrombelastography (TEG), a whole-blood viscoelastic assay, can identify orthopaedic trauma patients at 4-fold increased risk for in-hospital VTE, and cytokines are inflammatory mediators that can promote thrombus formation (interleukin [IL] 6, IL9, IL17A) or resolution (IL4, IL8, IL10). This study quantified serial hypercoagulability and inflammatory cytokine activity in patients with MBD, and compared these data in patients with and without VTE complications. We hypothesized that hypercoagulability and increased inflammatory cytokine activity would be associated with VTE.

METHODS: Following research ethics approval, consecutive adults with MBD who required orthopaedic surgery were enrolled into this single-centre, prospective cohort study. Exclusion criteria were primary bone cancer or current anticoagulation for an acute VTE. Serial whole blood analyses were performed over three months post-operatively using the TEG6s hemostasis analyzer (Haemonetics Corp) to quantify hypercoagulability and the MESO QuickPlex SQ 120MM (Meso Scale Diagnostics) for plasma cytokine analysis. Patients used pharmacological thromboprophylaxis for a minimum of four weeks post-operatively. Incidence of VTE (proximal deep vein thrombosis [DVT] or pulmonary embolism [PE]) was monitored throughout the study. Maximal amplitude (MA, a measure of clot strength) was evaluated using TEG, with hypercoagulability defined as MA ≥65 mm. Between-group comparisons and evaluation of post-operative changes compared to pre-operative measurements were performed using two-sample t-tests. One-sample t-tests were used to compare mean MA values in each group with the 65 mm threshold at each timepoint. Statistical significance was defined as $p < 0.05$.

RESULTS: Twenty-nine patients (17 female, 58.6%) with a mean age of 67 ± 11 years were included. Five patients (17.2%) developed VTE complications, including four patients with DVT and one patient with PE. Patients who developed VTE complications were hypercoagulable at all timepoints measured until VTE incidence (**Fig. 1**), with significantly elevated MA above the 65 mm hypercoagulability threshold pre-operatively ($p = 0.03$). Patients without VTE complications demonstrated hypercoagulability on POD3 ($p = 0.04$) and MA remained elevated until six weeks post-operatively (**Fig. 1**). Eighteen inflammatory cytokines were analyzed. Although higher overall cytokine levels were identified in patients with VTE, these increased levels were not significantly elevated compared to those without VTE (**Fig. 2**). However, in patients without VTE, significant increases in cytokine concentrations were observed on POD1 for IL17A ($p = 0.02$) and IL2 receptor antagonist (IL2RA, $p = 0.04$) compared to pre-operative measurements. Elevated monocyte chemoattractant protein-1 (MCP1) levels were also observed in the early post-operative period (POD1: $p = 0.04$, POD3: $p = 0.02$, POD5: $p = 0.03$).

DISCUSSION: Patients with MBD who had VTE demonstrated elevated hypercoagulability and systemic inflammation pre-operatively, supporting the utility of TEG-guided VTE risk stratification to distinguish the highest-risk patients. Hypercoagulability and elevated inflammatory cytokines persisted for six weeks post-operatively, suggesting that VTE risk may extend beyond the 4-week period during which thromboprophylaxis is commonly prescribed. Significantly elevated IL17A and MCP1, which have been linked to thrombus formation, suggest that hypercoagulability may be, in part, inflammatory-mediated. Sample size constraints of this pilot study limited observation of significant between-group differences. In addition, the heterogeneity of primary cancer types in patient participants could account for the variability in inflammatory responses and cytokine signatures. However, this study identified trends in post-operative hypercoagulability and quantified the concentration of inflammatory cytokines in patients with MBD for the first time.

SIGNIFICANCE/CLINICAL RELEVANCE: Pre-operative TEG analysis can identify patients with MBD at the highest risk for VTE. Hypercoagulability may be inflammatory-mediated, warranting investigation into the use of thromboprophylaxis agents that also have anti-inflammatory effects (i.e., aspirin).

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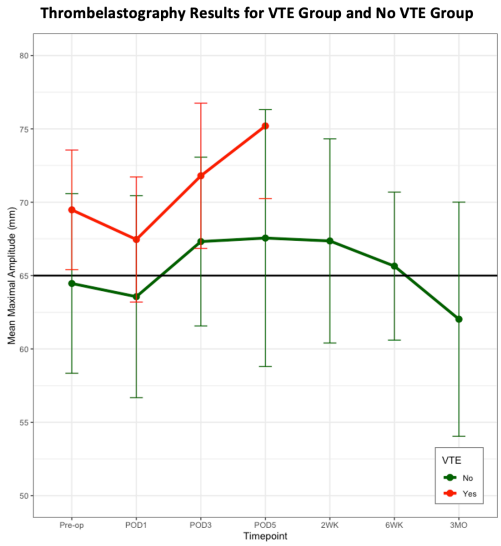

Figure 1. Mean maximal amplitude (MA) and standard deviation from serial thrombelastography. Hypercoagulability (MA ≥65 mm) was prolonged until 6-weeks post-operatively and elevated hypercoagulability was associated with venous thromboembolism (VTE).

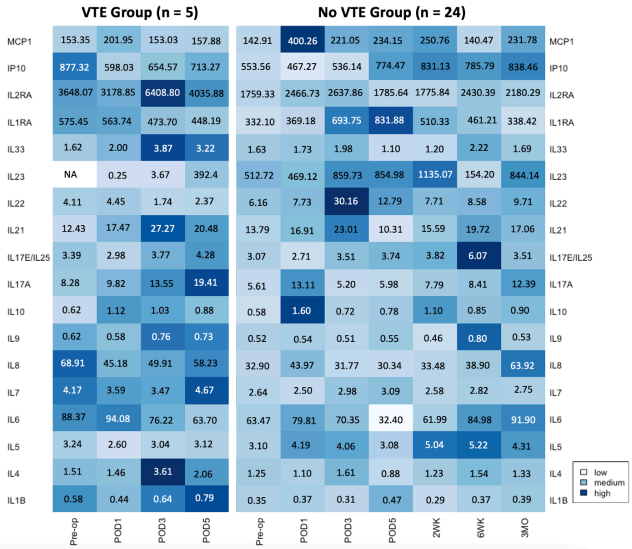

Figure 2. Mean concentrations (pg/mL) of biomarkers measured serially. Patients who developed VTE complications demonstrated elevated (moderate to high) cytokine activity pre-operatively, which increased following surgery. Elevated cytokine activity persisted until 3-months post-operatively.