Does Nicotine Account for Differences in Biomarker Profiles of Bone Healing? A Biochemical Survey of Smokers and Non-Smokers

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Purpose: Cigarette smoke contains many substances with the potential to negatively affect bone metabolism leading to an increased risk for delayed union and postoperative wound complications. Although the effects of smoking on fracture healing have been demonstrated in many studies, few studies have evaluated the physiologic basis of this observation. The primary goal of this study was to determine the baseline profile of biomarkers associated with bone healing in orthopaedic trauma patients who smoke and compare these with non-smokers. We hypothesized that selected biomarkers that are instrumental in bone healing will be different in smokers when compared to non-smokers. We also hypothesized that there will be a correlative relationship between cotinine level (a metabolite of nicotine) and biomarkers of bone healing.

Methods: 28 patients who sustained a long bone fracture or pelvis fracture that required operative fixation (age 43 ± 18 years; 62% M) were prospectively enrolled into this IRB-approved study. A blood sample was collected prior to fracture fixation and an enzyme-linked immunosorbent assay (ELISA) to evaluate selected biomarkers instrumental in bone healing, including transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), and bone morphogenetic protein-2 (BMP-2) was performed. ELISA was also performed to assess cotinine level in all patients. Demographics, medical history, and smoking history were queried from all patients.

Results: 10 smokers and 18 nonsmokers were enrolled. Average TGF-β in smokers was 35.27 ng/mL (standard deviation [SD] = 3.33), and 29.38 ng/mL (SD = 1.88) in non-smokers, which approached statistical significance (P = 0.1). Mean VEGF concentration was 147.89 pg/mL (SD = 29.60) in smokers, and 142.91 pg/mL (SD = 16.78) in non-smokers (P = 0.88). Mean BMP-2 concentration in smokers was 10.31 pg/mL (SD = 3.12), and 13.99 pg/mL (SD = 2.85) in non-smokers (P = 0.42). There was no significant correlation between cotinine level and TGF-β, VEGF, and BMP-2 (R2 = 0.0516, 0.0025, and 0.0018, respectively; P > 0.23). There was no significant correlation between pack history and TGF-β, VEGF, and BMP-2 (R2 = 0.1732, 0.0814, and 0.0665, P >0.23).

Conclusion: Smokers in our study demonstrated increased levels of TGF-β. This suggests a pro-inflammatory state associated with smokers versus non-smokers, which is expected. There was no difference in other markers of bone healing (VEGF and BMP2) between smokers/non-smokers. There was no correlation between cotinine level, pack history, and all markers of bone healing. This suggests that nicotine may not be the primary driver of the biochemical effects of smoking on bone healing. Further prospective longitudinal studies will help delineate smoking's deleterious mechanism to bone healing.