

# Changes in Bone Turnover Markers During Endurance Training and Implications for Bone Stress Injury

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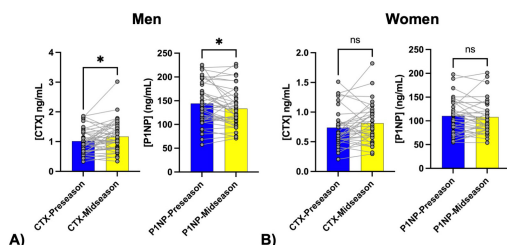
**INTRODUCTION:** Exercise is an important modulator of human health, and mechanical loading positively impacts bone mass by enhancing osteoblast-mediated formation. Interestingly, elevated bone turnover has been observed after the onset of aerobic exercise, with a heightened resorptive response sustained beyond exercise cessation. The relationship between the acute elevation in bone resorption markers during exercise and chronic bone remodeling over time remains unclear. Elite runners training at high volumes and intensities may be at risk for accumulated net negative bone balance over the course of a season, which may influence risk of bone stress injury (BSI). The purpose of this study was to prospectively evaluate markers of bone turnover in elite endurance athletes over multiple competitive seasons to determine whether prolonged exercise is associated with changes in bone balance, BSI detection, and BSI risk.

**METHODS:** In this IRB approved study, male, and female distance runners from an NCAA D1 Cross Country program were enrolled over multiple seasons. Subjects provided overnight fasted blood samples prior to pre-season training camp (August) and a second sample was provided approximately 10-12 days prior to conference championships (October) (Fig. 1). Isolated plasma was assayed for markers of bone formation (P1NP) and resorption (CTX). Samples were excluded if sufficient volume wasn't collected for both assays, if subjects reported having not completed overnight fast, or if subjects reported strenuous morning exercise prior to blood draw. Bone mineral density (BMD) of the lumbar spine (LS) and total hip (TH) was assessed by DEXA. BSI rates were tracked longitudinally throughout the year including during cross country (fall), indoor track (winter), outdoor track (spring), and off-season (summer). Associations between bone turnover markers and BSI incidence were evaluated in subjects free from BSI for 6 months leading up to the initial blood draw. Participants were categorized as to whether they experienced no BSI, had at least one BSI between the two blood draws (BSI detection), or had at least one BSI within 3 or 6 months after the second blood draw (BSI risk prediction). Paired t-tests evaluated within-season changes in P1NP and CTX for men and women, while Mann-Whitney tests evaluated differences in P1NP and CTX change in subjects with BSI between both blood draws compared to non-fractured controls. Fisher's exact test evaluated associations between BSI and bone turnover marker status within 3 or 6 months. Significance was assessed at  $p < 0.05$  for all measures.

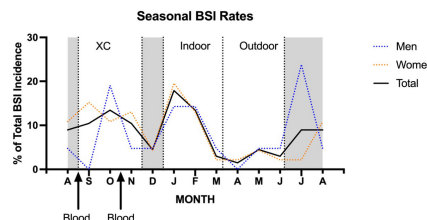
**RESULTS:** 41 male and 51 female unique participants enrolled over 4 academic years for a total of 193 athlete years of data. Of those participants, 77 eligible paired blood samples (40 male; 33 female) were assessed for bone turnover changes over the season. CTX increased ( $p < 0.05$ ) while P1NP decreased ( $p < 0.05$ ) in men but not women (CTX  $p = 0.14$ , P1NP  $p = 0.6$ ) through the season (Fig. 1). In both men and women, BMD Z-score was greater than zero at the TH, and less than zero at the LS ( $p < 0.05$  each, data not shown). BSI rates were elevated in the fall cross country season, falling to a minimum during December, and elevated during the first two months of indoor track before falling again during spring (Fig 2). 24 women were BSI-free for 6 months prior to first blood draw. 4 subsequently experienced BSI prior to the 2<sup>nd</sup> blood draw, 4 experienced a BSI within 3 months after the 2<sup>nd</sup> blood draw, and 2 experienced a BSI within 3-6 months thereafter. Changes observed in CTX and P1NP were not sensitive to detect fracture or fracture healing response in those runners with BSI between blood samples (data not shown). In contrast, subjects with BSI within 3 months after the second blood draw exhibited patterns of increasing CTX and sustained or reduced P1NP during the fall season (Fig. 3), albeit overlapping with non-fractured runners. In contrast, 38 men were BSI-free 6 months prior to the first blood draw. 1 subject fractured between blood draws, and 1 additional subject fractured within 3 months later, precluding a meaningful assessment of bone turnover status in male runners.

**DISCUSSION:** We observed a modest increase in bone resorption and decrease in bone formation in male, but not female distance runners during a 2 month period of high intensity training. In contrast to age- and sex-matched standards, men and women exhibited elevated BMD at the total hip, and reduced BMD at the lumbar spine. BSI incidence peaked in the fall, and changes in female bone turnover markers post-injury were no different than un-injured women during that time period, suggesting inability to detect focal remodeling associated with BSI. In contrast, women who suffered a BSI 3 months after paired blood draws exhibited substantial increases in serum CTX, and generally, no change, or a decline, in serum P1NP. In contrast, women who were able to elevate serum P1NP in the fall were protective from BSI for 3 months. Understanding factors governing anabolic and resorptive responses to long-term, endurance training may provide novel insight into skeletal adaptation and injury susceptibility in endurance athletes who are at greatest risk for BSI.

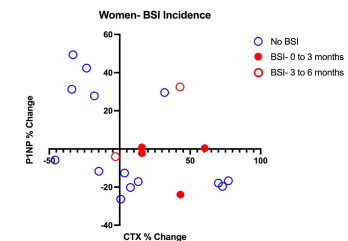
**SIGNIFICANCE/CLINICAL RELEVANCE:** Bone stress injuries represent a significant clinical burden, particularly in endurance athletes. While resistance-based exercise is generally considered anabolic to bone, understanding the skeletal response to long-term aerobic endurance training remains largely unexplored, but may provide insight into high repetitive use injuries in this population.



**Figure 1:** Groupwise change in CTX and P1NP in A) men and B) women reflecting changes in systemic bone resorption and formation between blood draw 1 (August) and 2 (October).



**Figure 2:** BSI incidence tracked annually for men and women during cross country (XC), indoor, and outdoor track and field. Blood sampling interval between August and October is shown.



**Figure 3:** Subjects sustaining BSI within 3-6 months of second blood draw show notable clustering of bone turnover marker changes during fall season toward a pro-resorptive, reduced bone formation phenotype.