Cross-correlation of Circulating Sclerostin over 24 hours to PTH, Phosphate and Bone Markers in Healthy Young Men

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Introduction

• With anti-resorptives dominating the current treatments of disorders involving bone loss such as osteoporosis, anabolic therapies involving sclerostin are likely to provide basis for a new strategy to generate high quality bone. A better understanding of the of sclerostin secretion and physiology is therefore necessary to define its role in bone metabolism.

• Sclerostin is predominantly secreted by the osteocytes that has been identified as a physiological inhibitor of bone formation.[1] We have successfully demonstrated that Sclerostin has a distinct circadian rhythm with a nocturnal peak.[2]

• The role of PTH and phosphate in bone metabolism have been demonstrated in no uncertain terms from previous studies. Serum phosphate in healthy individuals has been shown to have a regulatory role on PTH secretion, independent of its effects on calcium and vitamin D3.[3]

Aim

• To evaluate the pattern of Sclerostin secretion and its relation to other osteotropic hormones and bone markers (PTH, Calcium, Phosphate, βCTX and P1NP) in healthy young men, a tailored cross-correlation analysis was performed.

Materials and Methods

• 6 healthy young men were recruited. All patients had bone densitometric evaluation using a Prodigy Oracle Fan-Beam bone densitometer (GE Medical Systems, Giles, Buckinghamshire, UK).

• **Sclerostin** was measured by an enzyme linked immunoassay (Biomedica, Austria). All samples were assayed in duplicates. The intra and inter assay CV% being <5% and 12.3% respectively.

• **Serum PTH** was measured using the Advantage automated assay platform (Nichols Institute, San Juan Capistrano, CA, USA), with a detection limit of 0.5 pmol/L and intra- and inter assay CVs of <7% across the working range.

• Serum concentration of **type-I collagen-β C-telopeptide (CTX)** and **procollagen type-I amino-terminal propeptide (PINP)** were measured on the Elecsys automated platform, which uses electrochemiluminescence assays (ECLIA; Roche Diagnostics, Lewes, UK). The intra and inter assay CVs for β CTX were <4% and <5%, respectively, with a detection limit of 0.01 µg/L and the intra- and inter assay CVs for PINP, were <2% and <2.5%, respectively, across the working range, with a detection limit of 4 µg/L.

Statistical Analysis

• Cross-correlation analysis was performed to determine the relationships between the 24 hour profiles for Sclerostin, PTH, Calcium, Phosphate, βCTX and P1NP.

• Cross-correlation analysis determines the correlation between two time series of equal length that have been paired, data point by data point, then one of the time series is shifted by one or more time points (lag time) and the correlation process is repeated.

• Time series for the groups were derived by calculating the mean value at each time point for all subjects. To determine whether one time series led another, cross-correlation functions were computed at 12 lag points (up to 6h), based on evidence from previous studies.[4]
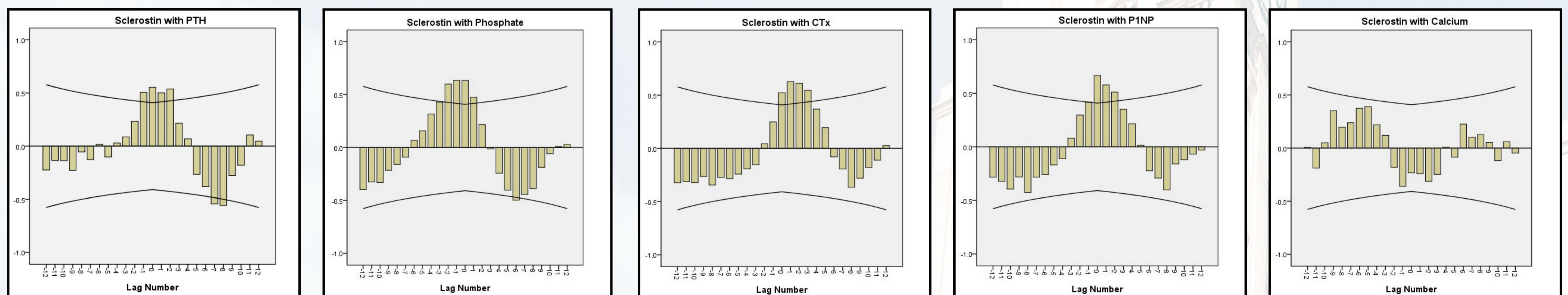
Results

• It has been demonstrated from previous studies using cross-correlation analysis in healthy individuals, that changes in serum phosphate precede the changes in PTH, which in turn precede the changes in bone resorption and formation.[3]

• Our results indicate that secretory patterns of sclerostin Vs. PTH and Calcium demonstrate no definite correlation during the 24hr period.

• A positive correlation was noted between sclerostin and phosphate, βCTX, P1NP with correlation co-efficients of 0.637, 0.627, 0.666 respectively. The changes in the sclerostin preceded βCTX by 1hr, but zero lags between sclerostin Vs phosphate and P1NP.

• The diurnal rhythms for CTx and PINP in healthy individuals demonstrated an early morning peak around 0500 h, with a nadir at around 1400 h, these peaks closely follow the patterns of sclerostin circadian providing further evidence to the crucial link between sclerostin and bone turnover.

Summary and Conclusions

• Despite the existence of a circadian rhythm for sclerostin it does not seem to either directly influence or be influenced by PTH secretion. It is unlikely that PTH is a modulator of sclerostin secretion.

• However, the strong correlation of sclerostin to bone markers and phosphate with a zero lag confirms that sclerostin is an important regulator of bone homeostasis .

• The absence of a strong correlation between PTH secretion and sclerostin does suggest the possibility of a direct influence of yet another independent factor on sclerostin circadian rhythm and bone homeostasis.

Fig. 1 Postive Correlations are demonstrated between Sclerostin and phosphate, βCTX, P1NP while there was no correlation noted between Sclerostin and PTH, Calcium.
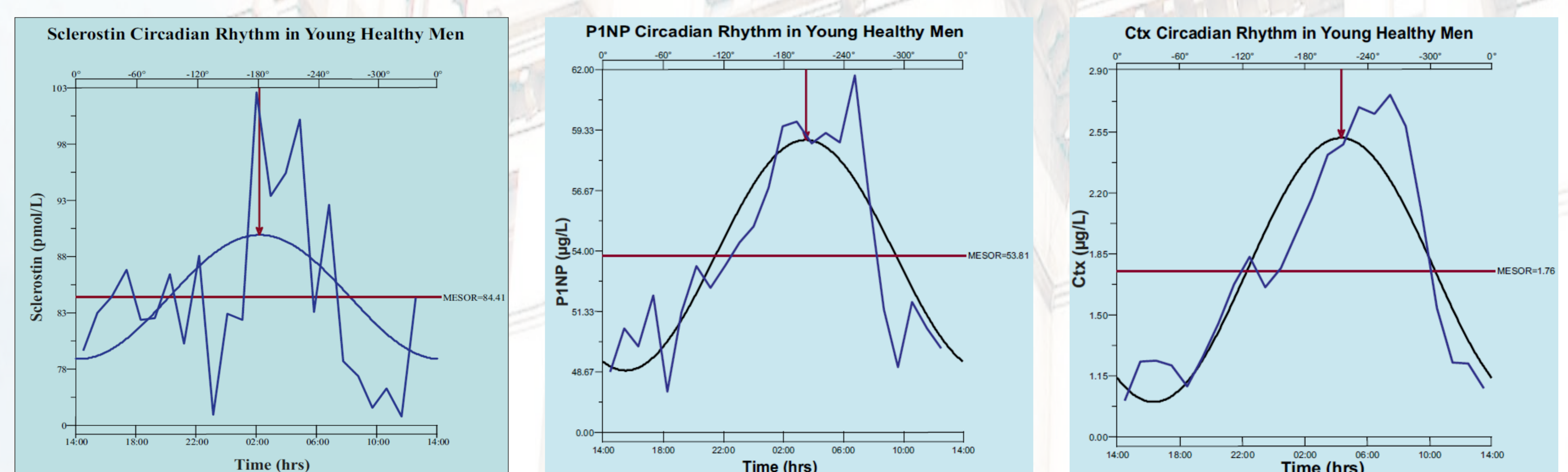
Fig. 2 An early morning peak (onset at 0100hrs) noted in the sclerostin secretion is closely followed by peak in the circulating concentrations of bone markers(P1NP and βCTX) at 0400 and 0500 respectively.

References

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