Evaluation of Serum Bone Turnover Markers in Renal Dialysis Patients

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ABSTRACT
Chronic renal dialysis patients have compromised bone status and increased bone turnover. This patient group presents special challenges in bone metabolism assessment. More recently, bone turnover markers (BTM) have demonstrated clinical utility in renal patients in spite of the retention and accumulation of some markers. This study compares recently available serum BTMs in 50 dialysis patients (23 males and 29 females) age 20 to 85 yrs with dialysis duration of 1 mo to 19 yrs (most under 3 yrs). Fasting blood samples were collected in the morning prior to one of three times weekly dialysis sessions.

Serum, urinary and alkali phosphatase (BSAP) were determined by ELISA. N-telopeptides (sNTx) were determined by ELISA (Osteometer BiTech A/S). Bone specific alkaline phosphatase by ELISA (BSAP, Metra Biosystems), osteocalcin by Elecsys (OC; Roche Diagnostics) and by IRMA (BSAP, ELISA, Osteocalcin; Elsevier). The correlation between serum telopeptides and BSAP was similar to that between osteocalcin and BSAP. Comparisons among the BTMs and PTH were listed below as correlation coefficients (r).

RESULTS

1. There was a significant correlation between serum telopeptides and BSAP (r = 0.79 – 0.90).
2. The correlation between serum telopeptides and BSAP was similar to that between OC and BSAP (r = 0.60).
3. PTH concentration and normalizing marker values with creatinine may enhance the discriminatory power of the BTM.

INTRODUCTION
Chronic renal failure patients on hemodialysis have compromised bone status. The standard tools for monitoring bone metabolism of these patients are invasive and expensive. This study investigates the potential of emerging serum markers of bone turnover as monitoring tools using a cohort of 50 renal dialysis patients.

1. The correlation between the sNTx and sCTx was strong. The correlation between the formation markers, BSAP and OC, and between the formation and resorption markers is poorer, partly due to different renal retention. Assays for the same analyte agreed well, however, the greatly elevated marker values present special demands on the assay design, such as analytic dynamic range, dilution linearity, assay precision and specificity and user friendliness. For example, further dilution was required in 10% of the samples in the sNTx assay, 20% in sCTx (i) and only 2% (one sample) in sCTx (o).

In summary, recently available serum BTMs may be useful in monitoring bone turnover status in the renal dialysis patients. Well-defined sample collection protocol and properly selected assays are important. Straying the patients using PTH concentration and normalizing marker values with creatinine enhance the discriminatory power of the BTM.

MATERIALS AND METHODS
Subjects
- 50 chronic hemodialysis patients with renal failure (21 males and 29 females) age 20 - 85 yr
- Dialysis treatment periods spanned 1 mo to 19 yrs with most subjects undergoing treatment for less than 3 yr.
- Fasting blood samples were collected in the morning prior to one of three times weekly dialysis sessions.
- Serum, urinary and alkali phosphatase (BSAP) were determined by ELISA. N-telopeptides (sNTx) were determined by ELISA (Osteometer BiTech A/S). Bone specific alkaline phosphatase by ELISA (BSAP, Metra Biosystems), osteocalcin by Elecsys (OC; Roche Diagnostics) and by IRMA (BSAP, ELISA, Osteocalcin; Elsevier).

1. The percent of samples that required dilution and reanalysis in this study was significant (listed below). These sample treatments have considerable practical implications.

Marker Comparison - Renal vs Non-renally Impaired
- Circulating bone turnover markers that are excrated through the kidneys were greatly elevated in the hemodialysis patients.
- Predictably, PTH was greatly elevated.
- Four patients with elevated TAP values (in red) also exhibited greatly elevated GGT, but not necessarily increased BSAP.
- The percent of samples that required dilution and reanalysis in this study was significant (listed below). These sample treatments have considerable practical implications.

Correlation Among Markers with and without Retention
- The relationship among markers was similar for the current dialysis population and the non-renally impaired population of comparable marker concentrations (n=185). Correlation (r) between OC and BSAP was 0.60. Renally cleared markers (telopeptide and OC) gave better correlations (r = 0.79 – 0.90).
- PTH correlation with BSAP was similar to that of other markers with BSAP (r = 0.60).
- When the ‘outlier’ TAP specimens were excluded, correlation between TAP and all other markers significantly improved. The excluded patients had greatly elevated GGT, indicating hepatic involvement.
- Adjustment of OC results by normalization with serum creatinine did not improve the correlation with BSAP or other markers.
- In contrast to earlier reports, little correlation between PTH and BSAP or TAP was observed.

2. The correlation between serum telopeptides and BSAP was similar to that between OC and BSAP (r = 0.60). Renally cleared markers (telopeptide and OC) gave better correlations (r = 0.79 – 0.90).
3. PTH correlation with BSAP was similar to that of other markers with BSAP (r = 0.60).
4. When the ‘outlier’ TAP specimens were excluded, correlation between TAP and all other markers significantly improved. The excluded patients had greatly elevated GGT, indicating hepatic involvement.
5. Adjustment of OC results by normalization with serum creatinine did not improve the correlation with BSAP or other markers.
6. In contrast to earlier reports, little correlation between PTH and BSAP or TAP was observed.

SUMMARY AND CONCLUSIONS
- The resorption markers, serum CTX and NTx correlated well and are greatly elevated in the dialysis cohort.
- The formation markers, BSAP and TAP, which are not retained by the kidney and OC, which is retained by the kidney are moderately correlated with the resorption markers.
- PTH may not be as useful as BSAP as a marker.
- The extent of marker elevation that is secondary to renal retention is unknown. This complicates interpretation of the data.
- Similar marker patterns between sCTx, sNTx, OC and BSAP are observed in this dialysis cohort and patients without renal impairment. Bone markers are potentially useful in assessing bone turnover status in renally impaired subjects.
- The bone marker assay design is especially important for use in this cohort. The Elecsys assays are precise, robust and easy to use.