**THE PREDICTIVE ROLE OF BIOCHEMICAL MARKERS IN BMD CHANGES IN MEN**

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**INTRODUCTION**

The use of biochemical markers of bone turnover, as indicators of overall bone metabolism, has been suggested as a potentially valuable clinical method in osteoporosis screening, diagnosis and monitoring the effects of different interventions. Biochemical markers reflect small changes in bone turnover of the entire skeleton in a shorter timeframe compared to the months or years that it can take to visualize distinct changes in bone mineral density (BMD) using absorptiometry methods. As there is a great need to identify persons at risk for osteoporosis, it would be useful to identify fast bone losers or slow bone losers.

The objectives of this study were to determine whether markers of bone formation, type I pro-collagen amino-terminal propeptide (PINP) and carboxy-terminal propeptide (PICP), and of bone resorption, type I collagen carboxy-terminal telopeptide (ICTP), are predictive of changes in BMD at the lumbar spine and femoral neck over a 5-year period, and also to determine the ability of urinary bone resorption marker amino-terminal telopeptide (NTx) to explain the variance in BMD change over the prior 5 years.

We hypothesized that the correlations of markers with either previous or future BMD changes (e.g., either over the prior or subsequent 5 years) would be higher than those found in a study using cross-sectional data (Donescu et al., 2005). The markers, which repre-sent bone turnover activity, were expected to better reflect relatively recent changes in bone mass than a measure taken at one point in time reflecting cumulative lifetime influences on BMD.

**METHODS**

**Study design.** Both prospective and retrospective cohort study designs were used to examine the ability of bone turnover markers to predict change in BMD over a 5-year period.

**Subjects.** The current study utilized data available from a larger project, in which twin pairs were selected and recruited from the population-based Finnish Twin Cohort. The sample is composed of 240 monozygotic (MZ) twins with data available for these markers and BMD. Twins ranged in age from 35–69 years (mean 49.7, SD 8.4). Subjects were excluded if they had a history of the following conditions in the prior year: thyroid, parathyroid disorders or hormone (cortisone or steroid) therapy (4); epilepsy (3); any skeletal disease or fracture (21); bed rest of more than 1 month (3); active cancer (3), or kidney or liver disorders (3). A total of 37 subjects were excluded, leaving 203 (82%) subjects for inclusion in analyses. The study protocols were reviewed and approved by the Ethical Committee at the University of Helsinki and the Human Research Ethics Board at the University of Alberta. Biochemical markers. Serum and urine specimens were collected in the morning and subsequently stored at -20°C to await analysis. PINP, PICP and ICTP were determined from serum by radioimmunoassay (Orion Diagnostica, Finland), with intra-assay CV 4.6-10.3% and inter-assay CV 3.1-10.8% for PINP; intra and inter-assay CV for PICP<6%; intra- and inter-assay CV for ICTP 2.8-6.2% and 4.1-7.9%, respectively. NTx was measured in urine using an ELISA resorption assay (Osteomark®; Ostex International) and was normalized to urinary creatinine (analytic intra-assay CV<5% and analytic inter-assay CV<8.0%).

**Bone mineral density** was measured with DXA (Lunar DPX, Madison, WI), at the L1-L4 vertebrae (CV 0.9%) and femoral neck (CV 1.5%).

**Data analysis.** Pearson coefficients assessed the correlation between change in spine and femoral neck BMD over the five years and baseline marker values. Multiple linear regression analyses were conducted to examine the ability of markers to explain change in BMD, with age, fat free weight, height and baseline BMD as possible confounding factors. A sample size of 70 subjects was calculated, thus the sample size of 203 subjects should be more than adequate.

**RESULTS**

Among the markers studied, NTx, a marker of bone resorption, measured at the follow-up correlated with the change in femoral neck BMD during the previous 5 years (r = -0.21, p = 0.006). NTx explained 3.8% of change in femoral neck BMD. The other variables (age, fat free weight, height) did not significantly add to the variance in femoral neck BMD, with the exception of baseline femoral neck BMD, which brought the total explained variance to 6.7%. Familial aggregation did not significantly add to the explained variance. Baseline levels of PINP, PICP, and of ICTP marker did not significantly correlate with the change in spine or femoral neck BMD in the subsequent five years. Although non-significant (p = 0.068), PINP levels explained 3.4% of the variance in spine BMD change when introduced in the regression model. Age explained an additional 5.9% of the variance. None of the other variables (fat free weight, height and spine BMD at baseline) was remotely significant. When added to the model, familial aggregation explained 23% of the variance.

**DISCUSSION**

The present study was conducted over a period of 5 years, and as far as we know is the longest longitudinal study on biochemical markers of bone turnover conducted in adult men. In this study of men, among the biochemical markers investigated, NTx was the only marker to correlate significantly with changes in BMD at the femoral neck, but not at the spine. Given the age of the subjects in the present study (35-69 years), a small variation in marker levels might be a factor affecting the results. However, in the present study group, NTx values were quite spread, as were the values for change in BMD. NTx, a marker of bone resorption measured at follow-up correlated with the change in BMD at the femoral neck during the previous 5 years (r = -0.21), similar to earlier cross-sectional findings (r = -0.3) (Donescu et al., 2005). Other longitudinal studies in men reported similar correlations between femoral neck BMD and the change in NTx (r = -0.26) (Chandani et al., 2000), or no correlation between baseline bone marker NTx and change in femoral neck and spine BMD Drake et al. (2003), and between PICP or ICTP and change in BMD (Sousa et al. 2002; Yoshimura et al. 1999). A limitation of longitudinal studies is that the measurement error in DXA can be expected to be greater relative to the BMD measure of change than for a single measure of BMD in a cross-sectional study.

In contrast to men, higher correlations between changes in BMD and biochemical markers like PICP, PINP and NTx have been reported in women. Several studies suggested that there are factors related to menopause that could contribute to a greater variation in bone metabolism in postmenopausal women when compared to premenopausal women or men (Miura et al., 1995; Rogers et al., 2000). The difference in the results from most studies of men, which found weak or no significant relationship between markers and BMD, and those of women, which found higher correlations, appear to reflect an influence of gender and hormonal differences. The biochemical markers express bone turnover in the whole skeleton, of which size is considerably influenced by gender (Vandervoort et al., 1999). Bone metabolism in men is less affected by the influence of estrogen than in women. Therefore, changes in bone mass in women might be of greater magnitude that those found in men, which might not be detectable through statistical methods, as they might also be comparable in size to the measurement error. There are also factors that might add to overall variation between different study results, like age-related changes, daily variations in individual levels of markers, age-related decrease in glomerular filtration or tubular reabsorption and metabolic rates that are not yet known for biochemical markers (Szulc and Delmas, 2001).

In summary, contrary to our hypothesis, the correlations of markers with previous or future BMD changes (over a 5-year period) were not higher than those found in a cross-sectional analysis. Baseline PINP, PICP and ICTP marker levels did not predict change in spine and femoral neck BMD in a group of men 35 to 69 years old. NTx levels explained a statistically significant yet quite limited portion of the variance in change in femoral BMD over the prior five years.

**REFERENCES**


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