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The association between bone turnover markers and kyphosis in community-dwelling older adults

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ABSTRACT

Purpose: Hyperkyphosis, accentuated curvature of the thoracic spine, is often attributed to osteoporosis, yet its underlying pathophysiology is not well understood. Bone turnover markers (BTM) reflect the dynamic process of bone formation and resorption. This study examined the association between serum BTM levels and kyphosis in community-dwelling older adults.

Methods: Between 2003 and 2006, 760 men and women in the Rancho Bernardo Study age 60 and older had blood drawn and kyphosis measured. Fasting serum was assayed for N-telopeptide (NTX) and procollagen type 1 n-terminal propeptide (P1NP), markers of bone resorption and formation, respectively. Participants requiring two or more 1.7 cm blocks under their head to achieve a neutral supine position were classified as having accentuated kyphosis. Analyses were stratified by sex and use of estrogen therapy (ET). Odds of accentuated kyphosis were calculated for each standard deviation increase in log-transformed BTM.

Results: Mean age was 75 years. Overall, 51% of 341 non-ET using women, 41% of 111 ET-using women, and 75% of 308 men had accentuated kyphosis. In adjusted models, higher P1NP and NTX were associated with decreased odds of accentuated kyphosis in non-ET using women (P1NP: OR = 0.78 [95% CI, 0.58–0.92]; NTX: OR = 0.68 [95% CI, 0.54–0.86]), but not in men or ET-using women ($p > 0.05$).

Conclusions: The selective association of higher bone turnover with reduced odds of accentuated kyphosis in non-ET using women suggests that elevated BTM were associated with a lower likelihood of hyperkyphosis only in the low estrogen/high BTM environment characteristic of postmenopausal women who are not using ET.

1. Introduction

Bone remodeling or turnover is the dynamic process of bone formation and resorption that is carried out by osteoblasts and osteoclasts throughout the life span (Marieb, 2001). Previous studies have shown associations between elevated or unbalanced turnover, as indicated by various bone turnover markers (BTM), and bone disorders such as osteoporosis and fracture (Cauley et al., 2012; Garnero, 2009; Tamaki et al., 2013). For example, a prospective study of 522 postmenopausal women reported that higher BTM were associated with an increased risk of vertebral fracture among women who were at least five years past menopause (Tamaki et al., 2013).

There are at least 15 different recognized biomarkers of bone turnover (Wheater et al., 2013), reflective of the bone metabolic processes formation and resorption. Although usually these processes are coupled, such that bone formation and bone resorption markers demonstrate parallel dynamics, a complete clinical picture is best obtained by measurement of both a resorption and a formation marker. A suitable bone formation marker for measurement in serum is P1NP, a cleavage product of Type 1 pro-collagen. There is low intra-individual variability of P1NP and a wide dynamic range in relation to clinical conditions. NTX, a cleavage product of Type 1 collagen, is an appropriate biomarker of bone resorption marker that is stable in serum; commercial assays provide measurements with the required precision.

Hyperkyphosis, accentuated curvature of the thoracic spine, has been estimated to affect up to 40% of community-dwelling older adults

Abbreviations: BTM, bone turnover markers; NTX, N-telopeptide; P1NP, procollagen type 1 n-terminal propeptide; ET, estrogen therapy; SOF, Study of Osteoporotic Fractures.

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and can be associated with poor health outcomes including impaired pulmonary function, increased falls and fractures, and mortality (Kado et al., 2003, 2004, 2007; Ryan and Fried, 1997). However, little is known about the mechanisms leading to hyperkyphosis. To date, there are no standard treatments available for people with accentuated kyphosis. Better understanding of the underlying pathophysiology of hyperkyphosis may help elucidate which types of interventions might be most promising to help individuals with hyperkyphosis.

To our knowledge, no studies have reported the association between bone turnover markers (BTM) and kyphosis. The purpose of this study is to examine the associations of accentuated kyphosis with serum collagen type 1 cross-linked N-telopeptide (NTX), a marker of bone resorption, and procollagen type 1 N-terminal propeptide (P1NP), a marker of bone formation, in a large sample of community-dwelling older men and women unselected for osteoporosis or kyphosis.

2. Materials and methods

2.1. Participants

Between 1972 and 1974, 6629 adult residents from Rancho Bernardo, a largely white, middle class community in southern California were enrolled in a cohort study of healthy aging. Between August 2003 and January 2006, 870 surviving, ambulatory participants attended a clinic visit designed to study osteoporosis and other age-related disorders. The study sample included 760 participants (308 men and 452 women) who remained after excluding 58 participants who were then younger than age 60, 39 missing measures of kyphosis, 11 without stored serum for BTM assessment, and two lacking information on estrogen therapy (ET).

The University of California, San Diego Human Research Protections Program approved this research protocol; all participants gave written informed consent prior to participation.

2.2. Procedures

During the 2003–2006 research clinic visit, morning fasting blood samples were obtained by venipuncture by a clinic nurse and frozen for later analysis. Kyphotic status was assessed by a trained radiology technician by placing 1.7 cm blocks under each participant's head. The number of blocks required to achieve a neutral position while lying supine on a flat surface was recorded; the greater the number of blocks required to achieve a neutral position, the more accentuated the angle of kyphosis. Details of this method of measuring kyphosis have been previously described (Kado et al., 2004).

Height and weight were also measured by a nurse using a calibrated stadiometer and balance beam scale with participants wearing light clothing and without shoes. Maximum waist girth was measured as an estimate of central obesity; body mass index (BMI; kg/m^2) was calculated as an estimate of overall obesity.

Total hip bone mineral density (BMD; g/cm^2) was measured using dual x-ray absorptiometry on a DXA Hologic 1000 (Waltham, MA), which was calibrated daily using a phantom with a precision error of 1.5% or less.

A self-administered survey was used to obtain information on smoking history (never/ever), alcohol intake (drinks per week), exercise ≥3 times per week (no/yes), education and history of physician-diagnosed comorbidities (stroke, diabetes, emphysema, chronic bronchitis, arthritis, Parkinson's disease, and spine fracture). Information on current medication and supplement use, including ET in women, was obtained by a nurse who validated with medication containers and prescriptions brought to the clinic for that purpose.

In 2008, serum NTX (BCE/l) was measured at SPD Development Company Limited (Bedford, UK) using the Osteomark ELISA (Unipath Ltd, UK); serum P1NP (μg/L) was measured by (UniQ, Orion Diagnostica) at Orion Diagnostica Oy (Oulu, Finland). Intra- and interassay coefficients of variation ranged from 2–6%.

Education level was categorized into high school or less, some college, a college degree or more. Alcohol intake was dichotomized into heavy drinking (yes/no) using sex-specific criteria; men consuming 21 or more drinks per week (three or more drinks per day) and women consuming 14 or more drinks per week (two or more drinks per day) were considered heavy drinkers based on the USDA definition of moderate drinking as up to one drink per day for women and up to two drinks per day for men (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2010).

2.3. Statistical analysis

All analyses were sex-specific due to differences between men and women in weight, height, and BMD; analyses of women were stratified by ET use due to the known effect of exogenous estrogen on bone turnover. Bivariate analyses to detect differences in covariates between those with normal versus accentuated kyphotic status were performed using age-adjusted logistic regression. Covariates with age adjusted $p < 0.25$ were included in saturated multivariate logistic regression models to examine the association between P1NP and NTX with kyphotic status (normal/accentuated) in each stratum. Covariates not significant at $\alpha = 0.05$ were removed from the saturated model. These variables were then placed back into the model one-by-one to assess for possible inclusion and/or confounding. Confounding was considered present if the effect size of the marker changed by a magnitude of 0.5 or more. Effect modification by use of osteoporosis medications was assessed by including an interaction term in the final model. Odds ratios from these logistic regression models represent the odds of accentuated kyphosis for each standard deviation increase in continuous variables.

Normal kyphotic status was defined as the use of 0 or 1 block to achieve a neutral supine position; those requiring 2 or more blocks were defined as having accentuated kyphotic status. This cut point was determined based on observed differences in physical function during exploratory analysis. NTX and P1NP levels were not normally distributed and were log transformed for all analyses; reported values are geometric means.

Statistical analyses were conducted using SPSS (version 19.0, SPSS Inc., Chicago, IL) and SAS (version 9.2, SAS Institute, Cary, NC). Statistical significance was defined as two-sided $p < 0.05$ for all tests.

3. Results

Mean age of the study sample was 75 years (range = 60–100). Prevalence of accentuated kyphotic status differed significantly between the three study groups ($\chi^2 = 55.813$, $p < 0.001$) but did not differ significantly between the non-ET using and ET-using women ($\chi^2 = 3.610$, $p = 0.057$); 51% of 341 non-ET using women, 41% of 111 ET-using women, and 75% of 308 men had accentuated kyphosis. Levels of both bone turnover biomarkers also differed significantly across the three study groups (ANOVA $p < 0.001$ for NTX and P1NP); NTX and P1NP levels were highest in non-ET using women (geometric means [GM] = 1.154 and 1.590, interquartile ranges [IQR] = 1.050–1.256 and 1.442–1.744), intermediate in men (GM = 1.113 and 1.521, IQR = 1.015–1.208 and 1.397–1.648), and lowest in ET using women (GM = 1.080 and 1.448, IQR = 0.993–1.146 and 1.280–1.603).

Age-adjusted comparisons of characteristics for each group by kyphotic status are shown in Table 1. NTX and P1NP were significantly lower in non-ET using women with accentuated kyphosis compared with their non-kyphotic counterparts, but did not differ by kyphotic status in men or ET using women. Men with accentuated kyphosis were significantly younger and weighed more than those with normal kyphotic status, but did not differ by mean height, BMI, total hip BMD, use of medications, or any behavioral or lifestyle characteristics. Non-ET using women with accentuated kyphosis weighed more, had higher