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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

Table 1
Comparisons of characteristics by kyphotic status in men and women aged 60 and older; Rancho Bernardo, CA (2003–2006).

	Men (n = 308)			Non-ET using women (n = 341)			ET using women (n = 111)		
	0–1 block (n = 77)	2+ blocks (n = 231)	p[a]	0–1 block (n = 167)	2+ blocks (n = 174)	p[a]	0–1 block (n = 65)	2+ blocks (n = 46)	p[a]
Characteristic, M (SD)									
NTX, BCE/l[b]	13.5 (1.4)	12.9 (1.4)	0.507	15.1 (1.4)	13.5 (1.4)	0.003	12.3 (1.5)	11.8 (1.4)	0.510
P1NP, μg/L[b]	35.5 (1.6)	32.4 (1.6)	0.095	41.7 (1.6)	36.3 (1.7)	0.026	28.2 (1.8)	27.5 (1.6)	0.982
Age, years	77.4 (9.9)	73.5 (6.6)	<0.001	75.6 (9.3)	75.9 (8.0)	0.749	72.4 (9.3)	75.0 (8.0)	0.120
Height, in	67.9 (2.9)	68.9 (2.5)	0.108	63.0 (2.3)	62.9 (2.5)	0.922	63.3 (2.3)	63.2 (2.1)	0.635
Weight, lb	171.7 (24.9)	184.1 (28.3)	0.024	138.1 (22.6)	146.7 (28.5)	0.002	140.4 (26.3)	155.1 (32.7)	0.004
BMI, kg/m^2	26.1 (2.9)	27.2 (3.7)	0.083	24.5 (3.9)	26.0 (4.9)	0.001	24.6 (4.4)	27.1 (4.7)	0.004
Waist girth, cm	96.3 (9.0)	99.0 (14.6)	0.144	81.1 (10.1)	86.2 (16.8)	0.001	80.6 (10.8)	89.5 (23.7)	0.013
Total hip BMD, mg/cm^2	0.92 (0.14)	0.95 (0.14)	0.308	0.78 (0.13)	0.78 (0.14)	0.937	0.87 (0.12)	0.89 (0.12)	0.246
Characteristic, % yes									
Education level			0.664			0.479			0.693
≤HS diploma	15	12		31	36		26	24	
Some college	30	24		41	35		38	47	
≥College degree	55	64		28	29		36	29	
Osteoporosis med use	4	6	0.504	25	34	0.062	9	15	0.454
CA^{2+} supplement use	39	29	0.108	64	54	0.077	71	54	0.097
Vit D supplement use	30	24	0.245	45	43	0.673	54	46	0.479
Ever smoked	53	61	0.188	40	52	0.021	42	50	0.308
Heavy alcohol intake[c]	3	7	0.298	8	14	0.081	6	11	0.405
Exercise ≥3 times/week	77	81	0.583	73	62	0.038	75	59	0.091
History of comorbidities[d]	35	39	0.237	34	43	0.093	35	35	0.825

[a] *p*-Value is age adjusted.
[b] Values are log-transformed.
[c] Heavy alcohol intake defined as 21 drinks or more per week for men and 14 drinks or more per week for women.
[d] Self-reported history of stroke, diabetes, emphysema, chronic bronchitis, arthritis, Parkinson's disease, and/or clinical spinal fracture.

BMI and waist girth, were more likely to have ever smoked, and were less likely to exercise three or more times per week. ET using women with accentuated kyphosis weighed more, had higher BMI and waist girth, but did not differ in any behavioral or lifestyle characteristics from those with normal kyphotic status.

Table 2 shows the association of BTM with kyphotic status in women by ET use. Among non-ET using women, higher P1NP and NTX were each independently associated with 22 to 32% lower odds of accentuated kyphosis in age-adjusted and fully adjusted models. Additional sequential adjustment for osteoporosis medication use and calcium supplement use did not materially alter the results (data not shown). Among ET using women, no significant associations were found between BTM and kyphotic status. Higher BMI was independently associated with increased odds of accentuated kyphosis in women, regardless of ET use.

Table 3 shows the association of bone formation and resorption markers with kyphotic status in men. Neither NTX nor P1NP were associated with kyphotic status in men in either the age-adjusted or fully adjusted models. Lower age and higher weight were each independently associated with increased odds of accentuated kyphosis in men.

4. Discussion

Because hyperkyphosis in older persons is associated with several adverse outcomes and has no standard clinical treatment, it is important to investigate potential mechanisms for this disorder that might provide

Table 2
Associations of bone turnover markers with accentuated kyphosis; results of multivariate logistic regression[a] models in women aged 60 and older; Rancho Bernardo, CA (2003–2006).

Marker type	Model	Variable	Non-ET users			ET users		
			OR	95% CI	p-Value	OR	95% CI	p-Value
Bone formation	P1NP – age adjusted			n = 341			n = 111	
		Log P1NP, μg/L (SD)	0.78	0.62–0.97	0.026	1.00	0.68–1.45	0.982
		Age, years (SD)	0.99	0.80–1.24	0.957	1.35	0.92–1.98	0.121
	P1NP – fully adjusted			n = 340			n = 111	
		Log P1NP, μg/L (SD)	0.73	0.58–0.92	0.007	0.92	0.62–1.37	0.688
		Age, years (SD)	1.04	0.83–1.30	0.758	1.46	0.98–2.19	0.065
		BMI, kg/m^2 (SD)	1.53	1.22–1.94	<0.001	1.88	1.23–2.86	0.003
		Ever smoked, yes	1.75	1.12–2.72	0.014			
Bone resorption	NTX – age adjusted			n = 341			n = 111	
		Log NTX, BCE/l (SD)	0.71	0.57–0.89	0.003	0.88	0.59–1.30	0.510
		Age, years (SD)	1.07	0.86–1.33	0.530	1.36	0.93–1.99	0.114
	NTX – fully adjusted			n = 340			n = 111	
		Log NTX, BCE/l (SD)	0.68	0.54–0.86	0.001	0.83	0.55–1.26	0.377
		Age, years (SD)	1.13	0.90–1.42	0.290	1.48	0.99–2.21	0.059
		BMI, kg/m^2 (SD)	1.51	1.19–1.90	<0.001	1.89	1.24–2.88	0.003
		Ever smoked, yes	1.76	1.12–2.75	0.013			

[a] The dependent variable reference category is normal kyphotic status (0–1 blocks).

Table 3
Associations of bone turnover markers with accentuated kyphosis; results of multivariate logistic regression models[a] in men aged 60 and older; Rancho Bernardo, CA (2003–2006; n = 308).

Marker type	Model	Variable	OR	95% CI	*p*-Value
Bone formation	P1NP – age adjusted	Log P1NP, μg/L (SD)	0.79	0.61–1.04	0.095
		Age, years (SD)	0.60	0.46–0.78	<0.001
	P1NP – fully adjusted	Log P1NP, μg/L (SD)	0.78	0.59–1.02	0.071
		Age, years (SD)	0.67	0.51–0.89	0.006
		Weight, lbs (SD)	1.46	1.07–2.01	0.018
Bone resorption	NTX – age adjusted	Log NTX, BCE/l (SD)	0.91	0.70–1.19	0.507
		Age, years (SD)	0.61	0.47–0.80	<0.001
	NTX – fully adjusted	Log NTX, BCE/l (SD)	0.93	0.71–1.22	0.600
		Age, years (SD)	0.68	0.52–0.91	0.009
		Weight, lbs (SD)	1.43	1.04–1.95	0.026

[a] The dependent variable reference category is normal kyphotic status (0–1 blocks).

insights for preventive interventions. To our knowledge, this is the first report of the association between BTM and kyphosis. We found that increased serum levels of markers of bone formation (P1NP) and resorption (NTX) were each independently associated with reduced odds of kyphosis in non-ET using women, and that serum levels of BTM were significantly higher in these women than in ET-using women or men. BTM were not associated with kyphotic status in men or ET using women.

High bone turnover is associated with osteoporosis (Manolagas, 2000) and fracture (Cauley et al., 2012; Tamaki et al., 2013), where bone loss results from increased activity and longer lifespan of osteoclasts coupled with osteoblast activity that is unable to compensate for the elevated resorption (Weitzmann and Pacifici, 2006). Results of the present study suggest that high bone turnover characterized by increased osteoclast and osteoblast activity may provide protection against the development of hyperkyphosis in non-ET using women. Wolff's law states that mechanical stress is able to trigger bone remodeling in humans (Marieb, 2001). Bennell (Bennell et al., 1997) observed elevated resorption markers in female power athletes and postulated that the "pattern of bone strain…could trigger local growth factors…which alter the remodeling process." It is conceivable that in some persons, age-related biomechanical forces that cause adverse loading conditions on the vertebral body (Ebbesen et al., 1999) could trigger a compensatory biological response with elevated bone turnover, reflecting active remodeling in attempts to avoid development of wedge compression deformities. This may be particularly evident in non-ET using women who have much lower levels of circulating estradiol than ET-using women and older men, who have comparable circulating estradiol levels. Interestingly, we have also recently reported that older men with lower endogenous estradiol levels have increased kyphosis, suggesting that hypoestrogenemia plays an important role in the development of hyperkyphosis (Kado et al., 2013a). Future research should address the influence of endogenous estradiol on bone turnover and kyphosis in both sexes.

Among the three study groups, ET using women had the lowest serum BTM as well as the lowest prevalence of accentuated kyphosis. It is possible that kyphosis is suppressed by ET use. Research in the Study of Osteoporotic Fractures has linked estrogen use with less kyphosis progression (Woods et al., 2014). This result has biological plausibility since bone turnover is known to be suppressed by ET use.

In this study of individuals aged 60 and older, relatively younger age in men was associated with higher odds of accentuated kyphosis that was likely due to survivor bias in the cohort. In our 2004 report (Kado et al., 2004), hyperkyphotic men from a previous clinic visit in the Rancho Bernardo Study had a significantly higher five-year mortality rate than non-kyphotic men. Thus, the current study population did not include those from the previous study who died and who also had the most extreme kyphotic posture. As both older age and kyphosis are associated with increased mortality rates, it is plausible that the majority of the oldest men in the present study were those who were the least affected by hyperkyphosis as compared with men in the younger age group who had the advantage of overall lower mortality rates. Why this protective association of greater age is not observed among the women in the present study is unclear.

Additionally, obesity (greater weight in men and higher BMI and weight in women) was associated with increased odds of accentuated kyphosis. These results are in agreement with our earlier study (Kado et al., 2013b) showing that greater weight was associated with more kyphosis in a cohort of 1000 women from the Study of Osteoporotic Fractures (SOF). The greater load that accompanies greater weight may adversely change posture, particularly in older adults who typically have less muscle mass for a given weight than younger persons (Lang et al., 2010).

In the present study, history of smoking was associated with a 75% increase in the odds of accentuated kyphosis among non-ET users. These findings contrast with those of our earlier study (Kado et al., 2013b), which found that current smoking was associated with less kyphosis among women in SOF. However, 80% of the participants selected for the SOF kyphosis study had to have serial x-rays completed over a 15-year period of follow-up and survivor bias may explain the disparate findings.

This study has some limitations. Due to its cross-sectional nature, these results can be considered only suggestive, describing associations rather than causation. The blocks method may lack sensitivity and specificity, although inter-rater reliability was 0.85 at the Rancho Bernardo clinic. Nonetheless, this study might have benefitted from a more precise measure of thoracic kyphosis, such as the Cobb angle, which was not calculated for most participants at this visit. The study might also have benefitted from additional clinical measures such as fracture history in relation to the measurement of bone turnover markers, radiographic presence of degenerative disc disease and vertebral fractures as well as further information about type of estrogen use. Lastly, the generalizability of our results is limited to non-Hispanic white, ambulatory, community-dwelling older adults.

This study also has several strengths. Sample sizes of the men and non-ET using women were relatively large. Information was collected on a wide range of covariates that could have altered BTM, kyphotic status, or both. Additionally, bone turnover markers were assayed using state of the art methods performed in experienced laboratories.

Results of this study suggest that elevated BTM are associated with a lower likelihood of hyperkyphosis only in the low estrogen/high BTM environment that is characteristic of postmenopausal women who are not using ET. These findings should be validated in other cohorts. The effect of estrogen on the mechanisms leading to kyphosis warrant further research so that interventions can be developed to treat or prevent hyperkyphosis.

Conflict of interest

Dr. Sarah Johnson is a Senior Research Scientist at SPD Development Company Limited, the entity that performed the NTX assays.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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