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ORIGINAL ARTICLE

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Bone Turnover in Young Adult Men: Cross-Sectional Determinants and Associations With Prospectively Assessed Bone Loss

Charlotte Verroken,[1,2] Hans-Georg Zmierczak,[1] Stefan Goemaere,[1] Jean-Marc Kaufman,[1,2] and Bruno Lapauw[1,2]

[1]Unit for Osteoporosis and Metabolic Bone Diseases, Ghent University Hospital, Ghent, Belgium
[2]Department of Endocrinology, Ghent University Hospital, Ghent, Belgium

ABSTRACT

Biochemical markers of bone turnover are higher in young adult men than in middle-aged men or young adult women. Nonetheless, little is known about the determinants and clinical significance hereof. The present study examined determinants of serum bone turnover markers in men around peak bone mass age, and explored whether bone turnover at this age predicts subsequent changes in bone mass. We used cross-sectional and longitudinal data from 973 and 428 healthy men, respectively, aged 25 to 45 years at baseline, including baseline procollagen type I amino-terminal propeptide (P1NP), osteocalcin, and C-terminal telopeptide of type I collagen (CTX) from fasting serum samples, baseline questionnaire-assessed physical activity levels, and baseline and follow-up dual-energy X-ray absorptiometry–derived areal bone mineral density (aBMD) and body composition. Mean follow-up time was 12.4 ± 0.4 years. At baseline, all bone turnover markers were inversely associated with total body fat mass ($\beta \leq -0.20$, $p < 0.001$), and positively with physical activity during sports activities ($\beta \geq 0.09$, $p \leq 0.003$), and, albeit not independently from fat mass, total body lean mass ($\beta \geq 0.20$, $p \leq 0.003$). Mean annual aBMD changes in the longitudinal cohort were $-0.19\% \pm 0.24\%$ at the total body, $-0.14\% \pm 0.42\%$ at the spine, $-0.49\% \pm 0.47\%$ at the femoral neck, and $-0.25\% \pm 0.37\%$ at the total hip (all $p < 0.001$). Higher bone turnover markers at baseline were associated with larger decreases in aBMD at all measurement sites ($\beta \leq -0.08$, $p \leq 0.081$ for P1NP; $\beta \leq -0.16$, $p \leq 0.002$ for osteocalcin; and $\beta \leq -0.21$, $p < 0.001$ for CTX). In conclusion, our findings show that sports activities and body composition, primarily fat mass, are the main identified determinants of bone turnover in men around peak bone mass age. Further, bone turnover at this age is an important determinant of subsequent changes in bone mass, with higher levels of bone turnover markers being associated with greater decreases in aBMD. © 2017 American Society for Bone and Mineral Research.

KEY WORDS: BIOCHEMICAL MARKERS OF BONE TURNOVER; DXA; AGING; BONE-FAT INTERACTIONS; BONE-MUSCLE INTERACTIONS

Introduction

Osteoporosis-associated fragility fractures remain a major health problem, leading to increased morbidity and mortality in both men and women.[1] The main determinants of the risk of developing osteoporosis include the acquisition of peak bone mass on the one hand, and the rate of subsequent bone loss on the other.[2] Bone mass acquisition occurs mainly during childhood and adolescence, with peak bone mass being achieved around the end of the third decade. This process is accompanied by high levels of bone turnover markers, reflecting linear growth at end-plates, modeling of the bone at the periosteum, and remodeling at endosteal surfaces.[3] After peak bone mass attainment, serum levels of bone turnover markers decrease rapidly in women only to rise again during and after menopausal transition, whereas they remain remarkably high in men, not reaching a nadir until the fifth or sixth decade of life.[4–6] The underlying mechanisms and clinical significance of these persistently high levels of bone turnover in young adult men are incompletely understood. High levels of bone turnover markers have been shown to predict greater increases in bone mass and size during bone acquisition,[7] but were associated with faster bone loss in postmenopausal women and middle-aged and elderly men,[8–10] whereas no studies have investigated this association in young adulthood. Furthermore, studies investigating possible determinants of bone turnover in adult men, including gonadal and adrenal sex steroids, insulin-like growth factor I (IGF-I), parathyroid hormone (PTH), and 25-hydroxyvitamin D [25(OH)D], are scarce and inconclusive.[3,5,11,12]

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Address correspondence to: Charlotte Verroken, MD, Unit for Osteoporosis and Metabolic Bone Diseases, Department of Endocrinology, Ghent University Hospital, De Pintelaan 185, 9K12IE, B – 9000 Gent, Belgium. E-mail: Charlotte.Verroken@UGent.be
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Additional Supporting Information may be found in the online version of this article.

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The present study aimed to examine determinants of serum bone turnover markers in young adult men around the age of peak bone mass attainment, and to explore whether bone turnover at this age predicts subsequent changes in bone mass. We hypothesized that (i) the relatively high levels of bone turnover markers in these men would be associated with parameters reflecting mechanical loading, and that (ii) they would predict early changes in bone mass after completion of growth.

Subjects and Methods

Study design and population

The present study is part of a population-based study designed to investigate determinants of peak bone mass and subsequent bone changes in men, including a cross-sectional and a longitudinal component and focusing on general lifestyle, sex hormone status, body composition, and genetic background. The detailed design of the cross-sectional study (SIBLOS) has previously been described.[13] Briefly, 1114 healthy men aged 25 to 45 years, who had a brother within the same age range also willing to participate, were recruited from the population registries of the semi-rural to urban communities around Ghent, Belgium, between March 2002 and July 2010. All participants completed questionnaires about medical history, medication use, education, smoking, and calcium intake.[14] After applying the exclusion criteria, including illnesses or medication use affecting body composition, sex hormone status or bone metabolism, 999 men were included in the study cohort. Five participants with nonfasting serum samples and 21 participants with a history of fracture within 1 year were additionally excluded from the present study, leaving a study sample of 973 men for the cross-sectional analyses. Recruitment for the ongoing longitudinal follow-up study (SIBEX) started in May 2014. In October 2016, 460 participants (of 678 invited) had been re-evaluated, corresponding to a participation rate of 67.8%. Reasons for loss to follow-up included death ($n = 4$), relocation ($n = 102$), or unwillingness to participate in the follow-up visit ($n = 115$). Among these 460 subjects, 32 were excluded after applying the same exclusion criteria that were used in the cross-sectional study (rheumatic or gastrointestinal inflammatory diseases, $n = 13$; myotonic dystrophy, $n = 1$ myasthenia gravis, $n = 1$ hemochromatosis, $n = 1$ malignancy, $n = 8$; gastric bypass, $n = 3$; systemic corticoid use for >3 months, $n = 7$; thyroxin therapy, $n = 3$; and bisphosphonate use, $n = 1$). Eleven of the remaining 428 participants were already excluded from the present cross-sectional analyses, leaving a study sample of 417 participants for the longitudinal analyses. The study protocol was approved by the ethical committee of the Ghent University Hospital and written informed consent was obtained from all participants. The SIBEX-study was registered on ClinicalTrials.gov (#NCT02997033).

Biochemical measurements

Venous blood samples were obtained between 8:00 a.m. and 10:00 a.m. after an overnight fast. Serum samples were stored at –80°C until batch analysis. C-terminal telopeptide of type I collagen [CTX; intraassay and interassay coefficient of variation (CV) $\leq$ 5.6%], procollagen type I N-terminal propeptide (P1NP; CV $\leq$ 10%), N-mid fragment of osteocalcin (CV $\leq$ 6.5%), and intact PTH (CV $\leq$ 4.3%) were measured using an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). 25(OH)D was determined after extraction by radioimmunoassay (DiaSorin, Stillwater, MN, USA; CV $\leq$ 11.3%). Commercial assays were used to determine serum levels of glucose (hexokinase method; CV $\leq$ 1.6%), insulin (CV $\leq$ 3.1%) and creatinine (CV $\leq$ 4.0%) (Roche Diagnostics, Mannheim, Germany), leptin (Linco Research, Inc., St. Louis, MO, USA; CV $\leq$ 8.3%), adiponectin (BioVendor LM, Brno, Czech Republic; CV $\leq$ 8.2%), IGF-I (Diagnostic System Laboratories, Webster, TX, USA and Cisbio Bioassays, Codolet, France; CV $\leq$ 7.5%), and sex hormone-binding globulin (SHBG; CV $\leq$ 7.8%) (Orion Diagnostica, Espoo, Finland). Total testosterone (T; CV $\leq$ 5.3%) and estradiol (E2; CV $\leq$ 7.2%) were determined by liquid chromatography-tandem mass spectrometry (AB Sciex 5500 triple-quadrupole mass spectrometer; AB Sciex, Toronto, Canada) as previously described.[15] Lower limits of quantification were 1 ng/dL for T and 0.3 pg/mL for E2. Free T and free E2 were calculated from T, E2, SHBG, and albumin concentrations using a previously validated equation derived from the mass-action law.[16,17] Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[18] Insulin resistance was evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR), calculated by multiplying insulin (mU/L) and glucose levels (mmol/L) and dividing the result by 22.5.[19]

Anthropometry, muscle parameters, body composition, and areal bone parameters

Body weight was measured to the nearest 0.1 kg in light indoor clothing without shoes. Standing height was measured to the nearest 0.1 cm using a wall-mounted Harpenden stadiometer (Holtain Ltd., Crymuch, UK). At baseline, physical activity was scored using the questionnaire developed by Baecke and colleagues.[20] This self-administered questionnaire is used to estimate an aggregate of the frequency, duration and intensity of habitual physical activities during work (work index), sports activities (sports index), and leisure time excluding sports (leisure time index). Using this scoring system, physical activity levels can range between 1 (minimum level) and 5 (maximum level). Grip strength (kg) was measured at the dominant hand using an adjustable hand-held standard grip device (JAMAR hand dynamometer; Sammons & Preston, Bolingbrook, IL, USA). Isokinetic peak torque of the biceps and quadriceps muscles (Nm) was measured at the dominant limbs using an isokinetic dynamometer (Biodex, New York, NY, USA). Body composition (including total body fat and lean mass) as well as areal bone parameters [including bone mineral content (BMC) and areal bone mineral density (aBMD) at the total body (without head), lumbar spine, and left proximal femur (total hip region and femoral neck)] were measured at baseline and follow-up using dual-energy X-ray absorptiometry (DXA), with a Hologic QDR-4500A device (software version 11.2.1; Hologic, Bedford, MA, USA). CVs for spine and hip phantoms (daily and weekly measurements, respectively) were 0.452% and 0.798% for aBMD, and 0.628% and 0.828% for BMC. Baseline and follow-up scans were performed by the same well-trained and dedicated technicians.

Statistical analyses

Descriptive data are expressed as mean $\pm$ standard deviation (SD) or median (25th to 75th percentile) when criteria for normality were not fulfilled. Skewed variables [bone turnover markers, 25(OH)D, PTH, sex steroids, total body fat and lean

mass, leptin, adiponectin, insulin, and HOMA-IR] were log-transformed in subsequent linear models. To evaluate the familial resemblance of bone turnover markers independently of age, conditional intraclass correlation coefficients (ICCs) were calculated from linear mixed-effect models including age as a fixed predictor, and multiplied with the proportion of the total variance not explained by age, calculated from unconditional models and models with age as a predictor. Cross-sectional associations between serum bone turnover markers and smoking behavior (smoker versus nonsmoker), season of visit, calcium intake, eGFR, hormonal parameters, physical activity, muscle parameters, body composition, and DXA parameters at baseline were evaluated using linear mixed-effects modeling, with list-wise deletion of missing data and a variance components residual correlation structure for random effects, taking into account the interdependence of measurements within families. Unless stated otherwise, cross-sectional analyses were adjusted for age, height, and weight. Changes in DXA measurements between baseline and follow-up were evaluated using linear mixed-effects modeling with an additional unstructured covariance structure for repeated measures. To determine if baseline bone turnover markers were independent predictors of subsequent changes in DXA parameters, linear mixed-effects modeling was performed with absolute annual changes in one of the DXA parameters as the outcome and one of the baseline bone turnover markers as the predictor variable, with additional adjustment for the respective baseline DXA measurement, baseline age and height, and baseline as well as changes in total body fat and lean mass. To estimate the proportion of aBMD and BMC changes explained by baseline bone turnover markers, R^2 values were calculated from covariance parameters derived from models including only baseline aBMD or BMC as the predictor variable (considered the null model), models additionally including baseline age, height, and baseline and changes in body composition, and models including these predictors plus one of the bone turnover markers. Continuous predictor and outcome variables were standardized in order to obtain standardized regression coefficients. Parameters of fixed effects were estimated using maximum likelihood estimation and reported as standardized regression coefficients (β) with their respective 95% confidence intervals (CIs). All analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). The Benjamini-Hochberg procedure was used to control for false discovery rate (set at $< 5\%$).[21] After correction, cut-off p values for statistical significance were <0.010 for cross-sectional and <0.036 for longitudinal analyses.

Results

General characteristics, body composition, muscle parameters, and biochemical measurements of the cross-sectional study sample are summarized in Table 1. The majority of the participants (55.1%) had a normal BMI, 36.6% were overweight, and 8.3% were obese. None of the participants were on antidiabetic drugs or had fasting glucose levels $\geq$7 mmol/L. Fat and lean mass relative to total mass were 19.6% ± 5.4% and 76.9% ± 5.1%, respectively. Mean values for work index, sports index, and leisure time index were 2.69 ± 0.75, 2.67 ± 0.78, and 2.68 ± 0.58; median calcium intake was 563 (426 to 741) mg daily. Mean serum creatinine was 0.95 ± 0.12 mg/dL, with none of the participants having an eGFR below 68.8 mL/min/1.73m^2.

Table 1. General Characteristics, Body Composition, Muscle Parameters, and Biochemical Measurements of the Cross-Sectional Study Population at Baseline (n = 973)

	Mean ± SD or median (25th to 75th percentile)
Age (years)	34.5 ± 5.5
Height (cm)	179.6 ± 6.5
Weight (kg)	80.8 ± 11.7
BMI (kg/m^2)	25.1 ± 3.5
Total fat mass (kg)	15.4 (11.6–19.8)
Total lean mass (kg)	61.3 (56.9–66.1)
Physical activity index	2.68 ± 0.44
Grip strength (kg)	52.7 ± 7.9
Biceps flexion torque (Nm)	56.7 ± 10.1
Quadriceps extension torque (Nm)	200.0 ± 42.4
Peak jump force (kN)	2.27 ± 0.37
P1NP (μg/L)	50.7 (41.6–63.6)
Osteocalcin (μg/L)	21.7 (18.4–26.3)
CTX (ng/mL)	0.41 (0.31–0.52)
PTH (ng/L)	33.4 (26.7–41.7)
25(OH)D (ng/mL)	18.7 (14.2–23.8)
Total T (ng/dL)	566.1 (454.6–689.5)
Total E2 (pg/mL)	20.00 (16.09–24.59)
IGF-I (ng/mL)	345.7 ± 119.2
Leptin (μg/L)	4.1 (2.6–6.8)
Adiponectin (mg/L)	8.3 (6.3–10.9)
Glucose (mmol/L)	4.7 ± 0.5
Insulin (pmol/L)	43.8 (31.3–62.5)
HOMA-IR	1.35 (0.90–1.93)

Physical activity was scored using the questionnaire as proposed by Baecke and colleagues;[20] levels can range between 1 (minimum level) and 5 (maximum level).

P1NP = procollagen type I N-terminal propeptide; CTX = C-terminal telopeptide of type I collagen; PTH = parathyroid hormone; 25(OH)D = 25-hydroxyvitamin D;T = testosterone; E2 = estradiol; IGF-I = insulin-like growth factor 1; HOMA-IR = homeostasis model assessment of insulin resistance.

Cross-sectional determinants of serum bone turnover markers and associations with areal bone parameters

Bone turnover markers were highly intercorrelated, with correlation coefficients ranging between 0.63 (for P1NP and CTX) and 0.73 (for P1NP and osteocalcin; all $p < 0.001$). Independently of age, familial resemblance explained 34% of the variance in P1NP, 29% of the variance in osteocalcin, and 28% of the variance in CTX. In unadjusted analyses, all bone turnover markers were inversely associated with age (β = –0.37 for P1NP, β = –0.38 for osteocalcin, and β = –0.34 for CTX; all $p < 0.001$) and weight (β = –0.19, β = –0.12, and β = –0.16; all $p < 0.001$). We detected no seasonal variation in serum levels of bone turnover markers ($p \geq 0.142$), and besides a trend toward lower osteocalcin in smoking versus nonsmoking participants (geometric means 21.0 ± 0.25 versus 22.0 ± 0.12 μg/L, $p = 0.012$), bone turnover markers were not associated with smoking behavior ($p \geq 0.072$), calcium intake ($p \geq 0.405$), or eGFR ($p \geq 0.068$).

Cross-sectional associations of bone turnover markers with body composition, muscle parameters, and biochemical measurements are shown in Table 2 (Model A). Serum bone turnover

Table 2. Cross-Sectional Associations of Serum Bone Turnover Markers With Body Composition, Physical Activity, and Biochemical Measurements at Baseline ($n = 973$)

	P1NP		Osteocalcin		CTX	
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Model A						
Total body fat mass	−0.25 (−0.36 to −0.15)	<0.001	−0.20 (−0.31 to −0.09)	<0.001	−0.24 (−0.35 to −0.13)	<0.001
Total body lean mass	0.22 (0.09 to 0.35)	0.001	0.20 (0.07 to 0.33)	0.003	0.30 (0.17 to 0.43)	<0.001
Sports index	0.13 (0.07 to 0.19)	<0.001	0.10 (0.05 to 0.16)	<0.001	0.09 (0.03 to 0.15)	0.003
PTH	0.06 (0.004 to 0.12)	0.037	0.11 (0.05 to 0.16)	<0.001	0.07 (0.009 to 0.13)	0.023
Leptin	−0.12 (−0.21 to −0.04)	0.004	−0.13 (−0.21 to −0.05)	0.002	−0.10 (−0.18 to −0.01)	0.028
Glucose	−0.08 (−0.14 to −0.02)	0.008	−0.06 (−0.12 to −0.004)	0.036	0.002 (−0.06 to 0.06)	0.948
Model B						
Total body fat mass	−0.15 (−0.22 to −0.08)	<0.001	−0.19 (−0.26 to −0.12)	<0.001	−0.21 (−0.28 to −0.14)	<0.001
Total body lean mass	0.04 (−0.04 to 0.12)	0.357	−0.04 (−0.11 to 0.04)	0.389	0.03 (−0.05 to 0.11)	0.474
Sports index	0.10 (0.05 to 0.16)	<0.001	0.08 (0.03 to 0.14)	0.004	0.06 (0.001 to 0.12)	0.046

Model A: model including one of the bone turnover markers as the outcome and total body fat mass, total body lean mass, sports index, PTH, leptin, or glucose as the predictor variable, with additional adjustment for age, height and weight. Model B: model including one of the bone turnover markers as the outcome and total body fat mass, total body lean mass, and sports index as the predictor variables, with additional adjustment for age and height. Sports index was calculated using the questionnaire as proposed by Baecke and colleagues.[20]

P1NP = procollagen type I N-terminal propeptide; CTX = C-terminal telopeptide of type I collagen, PTH = parathyroid hormone.

markers were positively associated with total body lean mass and inversely with total body fat mass. In addition, all bone turnover markers were positively associated with sports index, whereas we observed no associations with either total physical activity or work or leisure time index, nor with any of the parameters reflecting muscle strength (all $p \geq 0.075$). When fat and lean mass were included in the same model, fat mass remained an independent predictor of bone turnover ($\beta = -0.19$ for P1NP, $\beta = -0.22$ for osteocalcin, and $\beta = -0.26$ for CTX; all $p < 0.001$), whereas the associations with lean mass lost significance (all $p \geq 0.095$). Additional adjustment for sports index did not alter these results (Table 2, Model B). Bone turnover markers were generally positively associated with PTH and inversely with leptin. In addition, P1NP was inversely associated with fasting glucose, although this association weakened after adjustment for body composition (ie, total body lean and fat mass) instead of weight ($\beta = -0.07$, $p = 0.013$). Besides weak positive associations of P1NP with SHBG (age, height, and body composition-adjusted $\beta = 0.08$, $p = 0.009$) and of CTX with IGF-I ($\beta = 0.11$, $p = 0.001$), we observed no associations of serum bone turnover markers with sex steroids, 25(OH)D, adiponectin, IGF-I, insulin, or HOMA-IR (all $p \geq 0.045$). Furthermore, bone turnover markers were not associated with aBMD or BMC at any of the measurement sites (all $p \geq 0.022$).

Longitudinal associations between baseline bone turnover markers and changes in areal bone parameters

Except for a small difference in baseline age (34.5 ± 5.5 versus 35.0 ± 5.4 years, $p = 0.008$) and P1NP levels [50.7 (41.6 to 63.3) μg/L versus 49.3 (41.4 to 62.8) μg/L, $p = 0.045$], the 417 participants for whom follow-up data were available did not differ from the total study population in terms of anthropometry, body composition, muscle parameters, DXA parameters, or bone turnover markers. Mean follow-up time was 12.4 ± 0.4 (range, 12.2 to 12.6) years. Changes in bone parameters between baseline and follow-up are summarized in Table 3. Younger age at baseline was associated with a larger aBMD decrease at the total body ($\beta = 0.11$, $p = 0.035$), and with larger aBMD and BMC decreases at the total hip ($\beta = 0.19$ and $\beta = 0.22$, both $p < 0.001$) and femoral neck ($\beta = 0.22$ and $\beta = 0.17$, both $p < 0.001$) (Fig. 1).

Table 4 and Fig. 2 display the associations between baseline bone turnover markers and changes in DXA parameters. Higher levels of osteocalcin and CTX at baseline were associated with

Table 3. Areal Bone Parameters at Baseline and Follow-Up ($n = 417$)

	Baseline	Follow-up	Annual change	Annual % change
Total body aBMD (g/cm^2)	1.111 ± 0.092	1.085 ± 0.091	−0.002 ± 0.003[a]	−0.19 ± 0.24
Total body BMC (g)	2349.1 ± 313.7	2314.9 ± 308.2	−2.9 ± 7.6[a]	−0.12 ± 0.31
Spine aBMD (g/cm^2)	1.060 ± 0.122	1.043 ± 0.128	−0.002 ± 0.004[a]	−0.14 ± 0.42
Spine BMC (g)	76.4 ± 12.3	75.8 ± 12.6	−0.06 ± 0.41[a]	−0.07 ± 0.53
Total hip aBMD (g/cm^2)	1.078 ± 0.137	1.043 ± 0.128	−0.003 ± 0.004[a]	−0.25 ± 0.37
Total hip BMC (g)	48.7 ± 7.8	48.7 ± 7.6	−0.002 ± 0.23	0.01 ± 0.45
Femoral neck aBMD (g/cm^2)	0.885 ± 0.129	0.829 ± 0.116	−0.005 ± 0.004[a]	−0.49 ± 0.47
Femoral neck BMC (g)	5.17 ± 0.82	4.85 ± 0.73	−0.03 ± 0.03[a]	−0.47 ± 0.53

Annual changes in areal bone parameters were calculated as the absolute change from baseline to follow-up divided by years of follow-up. Annual % changes were calculated as annual change divided by the respective baseline value, multiplied by 100.

aBMD = areal bone mineral density; BMC = bone mineral content.

[a]p for change < 0.001.

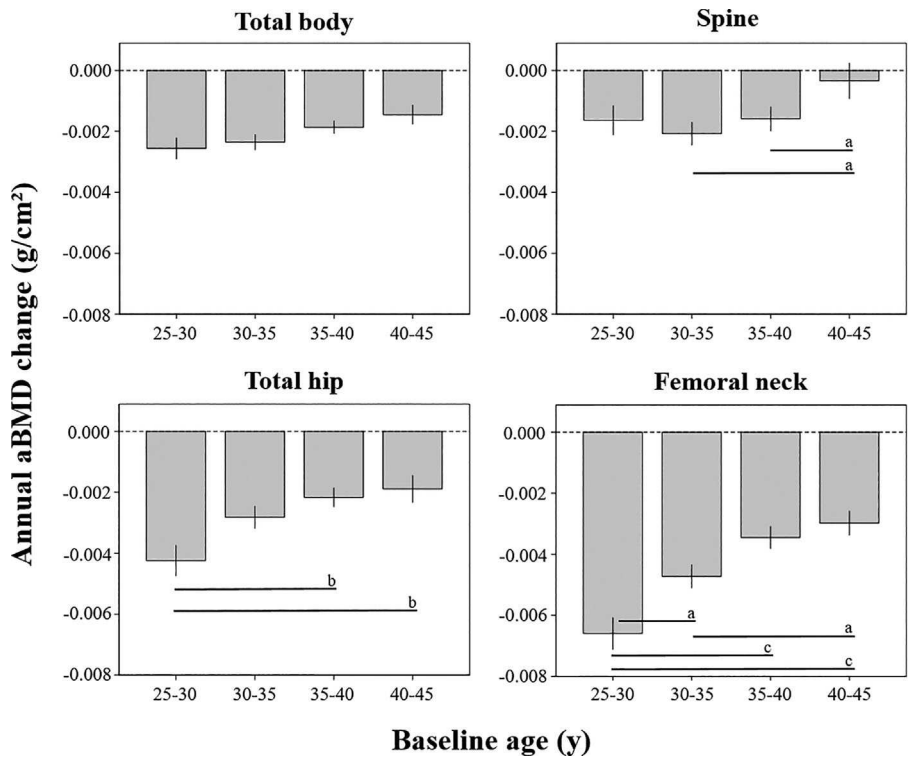

Fig. 1. Associations between baseline age and aBMD changes at the total body (minus head), spine, total hip, and femoral neck. Annual aBMD changes were calculated as the absolute change from baseline to follow-up divided by years of follow-up. Bars and whiskers represent mean annual aBMD change and standard error per age category. $^{a}p < 0.05$, $^{b}p < 0.01$; $^{c}p < 0.001$; analyses are adjusted for baseline aBMD value. aBMD = areal bone mineral density.

larger decreases in aBMD and BMC at all measurement sites. In addition, higher baseline P1NP levels were associated with larger decreases in aBMD and BMC at the total hip and spine. As compared to models including only baseline age, height, body composition, and changes in body composition as predictor variables, models additionally including one of the bone turnover markers increased the explained proportion of variance in aBMD and BMC changes with up to 8%, with the largest increases observed for models including CTX (Supporting Table 1). Results were largely unchanged after additional adjustment for baseline sports index or PTH. No interactions between the bone turnover markers and baseline age were observed for any of the DXA parameters.

Discussion

The present study investigated the determinants of serum bone turnover markers in men around peak bone mass age, as well as their association with subsequent changes in bone mass. Our results indicate that among a broad range of potential determinants and besides young age, body composition and physical activity during sports activities emerge as the most

Table 4. Associations of Baseline Bone Turnover Markers With Annual Changes in Areal Bone Parameters

	P1NP		Osteocalcin		CTX	
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Δ Total body aBMD	−0.13 (−0.23 to −0.03)	0.012	−0.20 (−0.30 to −0.10)	<0.001	−0.31 (−0.40 to −0.21)	<0.001
Δ Total body BMC	−0.11 (−0.21 to −0.01)	0.006	−0.17 (−0.27 to −0.07)	0.001	−0.24 (−0.33 to −0.15)	<0.001
Δ Spine aBMD	−0.13 (−0.23 to −0.02)	0.015	−0.16 (−0.27 to −0.06)	0.002	−0.27 (−0.36 to −0.17)	<0.001
Δ Spine BMC	−0.11 (−0.21 to −0.03)	0.044	−0.15 (−0.25 to −0.04)	0.028	−0.23 (−0.33 to −0.13)	<0.001
Δ Total hip aBMD	−0.08 (−0.16 to 0.01)	0.081	−0.16 (−0.24 to −0.07)	<0.001	−0.25 (−0.33 to −0.16)	<0.001
Δ Total hip BMC	−0.05 (−0.14 to 0.04)	0.300	−0.12 (−0.21 to −0.03)	0.011	−0.19 (−0.28 to −0.11)	<0.001
Δ Femoral neck aBMD	−0.08 (−0.17 to 0.01)	0.069	−0.16 (−0.24 to −0.07)	<0.001	−0.21 (−0.29 to −0.13)	<0.001
Δ Femoral neck BMC	−0.02 (−0.11 to 0.07)	0.628	−0.13 (−0.22 to −0.04)	0.005	−0.18 (−0.26 to −0.10)	<0.001

Analyses are adjusted for the baseline DXA parameter, baseline age, height, and total body lean and fat mass, and changes in lean and fat mass. Annual changes in areal bone parameters were calculated as the absolute change from baseline to follow-up divided by years of follow-up. P1NP = procollagen type I N-terminal propeptide; CTX = C-terminal telopeptide of type I collagen; aBMD = areal bone mineral density; BMC = bone mineral content.

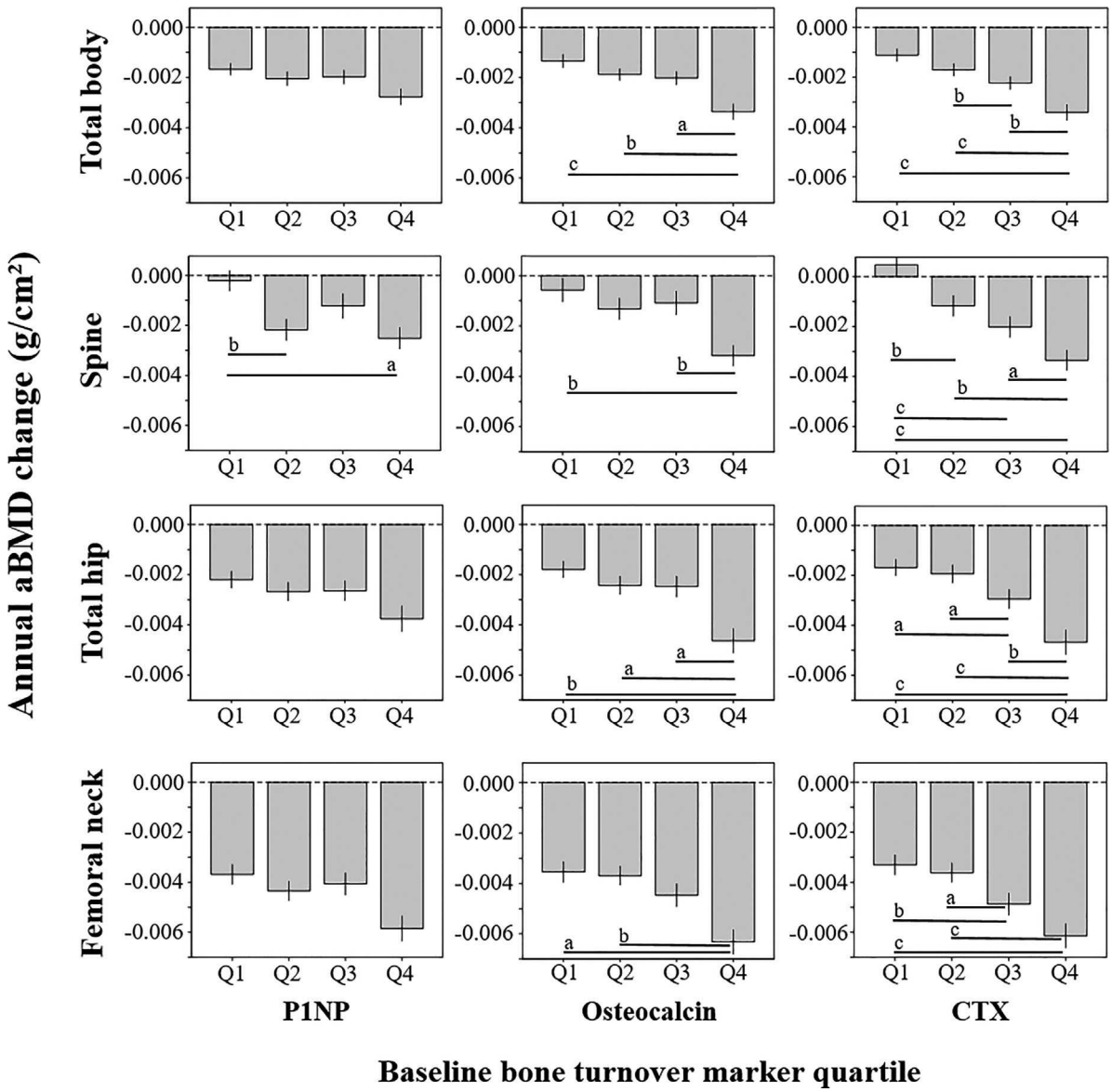

Fig. 2. Associations between baseline bone turnover markers and aBMD changes at the total body (minus head), spine, total hip, and femoral neck. Annual aBMD changes were calculated as the absolute change from baseline to follow-up divided by years of follow-up. Bars and whiskers represent mean annual aBMD change and standard error per quartile of baseline bone turnover markers. Quartile limits are 41.4 μg/L, 49.3 μg/L, and 62.8 μg/L for P1NP; 18.3 μg/L, 21.5 μg/L, and 25.7 μg/L for osteocalcin; and 0.31 μg/L, 0.42 μg/L, and 0.52 μg/L for CTX. [a]$p < 0.05$, [b]$p < 0.01$; [c]$p < 0.001$; analyses are adjusted for baseline aBMD value, baseline age, height, and weight, and weight change. aBMD = areal bone mineral density.

important determinants of bone turnover in young adulthood, with fat mass being inversely and sports activities being positively associated with serum levels of bone turnover markers. Furthermore, our longitudinal observations show that bone loss in young adult men starts early after peak bone mass attainment at all measurement sites, with higher levels of bone turnover around peak bone mass age predicting greater subsequent declines in aBMD.

In this population of young adult men, biochemical markers of bone turnover were inversely associated with age but remained remarkably high compared to levels described in premenopausal women,[22,23] corroborating previous observations that in men, bone turnover remains high after peak bone mass attainment and reaches a nadir only in the fifth or sixth decade.[4–6] Bone turnover showed a relatively strong familial resemblance with, independently of age, 28% to 34% of the variance being located at the family level. Although the present study was not designed to discriminate whether this familial resemblance is due to genetic or environmental factors, evidence from twin studies suggested an important genetic component.[24–28] Moreover, between-brother correlations of bone turnover markers in older men were comparable to those in our population, suggesting that the familial resemblance of bone turnover cannot be entirely accounted for by shared environmental factors.[29]

Partly corroborating our hypothesis, we observed positive associations of bone turnover with lean mass and physical activity during sports activities, but not with overall physical activity or parameters reflecting muscle strength. Moreover, associations with lean mass were no longer significant after adjustment for fat mass in multivariate models, suggesting that mechanical loading is not a major determinant of the high levels of bone turnover in men around peak bone mass age. In contrast, fat mass showed strong inverse associations with biochemical markers of bone turnover, which is in line with the lower levels of bone turnover observed in obese as compared to non-obese children and adults,[30–32] and with the observation that central adiposity was associated with lower bone formation in premenopausal women.[33] Given that men and women differ markedly in terms of body composition, with men having less fat and more lean mass as compared to women, these findings may at least in part explain the higher levels of bone turnover markers in young adult men as compared to women.

The mechanisms underlying the inverse association between fat mass and bone turnover remain to be unraveled, although a possible role may be attributed to an altered adipokine secretion. In line herewith, we and other authors described inverse associations between leptin levels and bone turnover markers.[30] Nonetheless, as the role of leptin in bone homeostasis is complex and serum leptin levels may merely be an index of the amount of fat mass rather than being directly involved in its effects, its putative effects on bone turnover merit further research.[34] Increases in body fat are also accompanied by changes in glucose metabolism, including increased fasting glucose levels and insulin resistance, which may in turn affect bone turnover. Whereas some studies indeed reported inverse associations of bone turnover markers with HOMA-IR,[31,35] we and others observed no association with HOMA-IR or fasting insulin levels,[30] and the observed association between P1NP and fasting glucose in our study lost significance after adjustment for body composition.

Although the timing is site- and sex-specific, peak bone mass is generally assumed to be achieved during the second or third decade of life.[36–39] To the best of our knowledge, our study is the first to specifically focus on the subsequent longitudinal bone changes in young adult men, showing decreases in aBMD at all measurement sites over a 12-year follow-up period. This is in line with previous data showing that in both men and women, trabecular bone loss starts early after peak bone mass attainment, although cortical bone has been suggested to remain fairly stable until midlife.[40,41] In addition, we showed that higher levels of bone turnover at baseline were associated with larger declines in aBMD and BMC, which is in parallel to what has been described in middle-aged and elderly populations.[8,9,42] Conversely, in men at the end of puberty, high bone turnover levels have been shown to be associated with larger increases in bone mass and size.[7] The differential relationship between levels of bone turnover markers and bone changes before and after peak bone mass attainment is explained by the fact that during growth, the net positive modeling and remodeling balance leads to bone accrual, whereas after peak bone mass attainment modeling declines and the remodeling balance shifts towards resorption, thus leading to net bone loss.[43,44] As the net changes associated with each remodeling cycle are small, the rates of bone gain and bone loss are more importantly driven by the remodeling rate.[45] Interestingly, we observed the largest decreases in aBMD and BMC in the youngest men. Therefore, we speculate that whereas the high rates of bone turnover in young men, mediated by sports activities and a favorable body composition, lead to an optimal acquisition of peak bone mass during growth, they predict a more rapid loss of bone mass soon thereafter.

Strengths of our study include the longitudinal design and the relatively large and well-characterized population-based sample of healthy men. Limitations include the inclusion of only male and primarily white subjects, the relatively low participation rate in the longitudinal study, and the lack of intermittent follow-up time points due to which possible initial increases in bone mass in the youngest participants may have been missed. However, as the largest bone losses were observed in the youngest men and associations of bone turnover markers with bone loss were consistent across the age range, the latter may have had little or no effect on our results. Although we identified significant determinants of bone turnover marker levels among a rather broad panel of potential determinants, we acknowledge that they explain only part of the variance in this population, and the persistence of high levels of bone turnover markers in young adult men after completion of bone maturation thus remains to be fully elucidated.

In conclusion, this study showed that in healthy adult men around peak bone mass age, sports activities and body composition, primarily fat mass, are the main identified determinants of bone turnover. In turn, bone turnover at this age is an important determinant of subsequent bone changes, with higher levels of bone turnover markers being associated with greater decreases in aBMD at several skeletal sites over a 12-year period. Thus, whereas high levels of bone turnover may lead to larger increases in bone mass during growth, our findings suggest that around peak bone mass age, they predict a more rapid bone loss.

Disclosures

All authors state that they have no conflicts of interest.

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Authors' roles: Study design: HGZ, SG, and JMK. Data collection: CV, HGZ, SG, JMK, and BL. Data analysis: CV and BL. Data interpretation: CV, HGZ, SG, JMK, and BL. Drafting manuscript: CV. Revising manuscript content: HGZ, SG, JMK, and BL. Approving final version of manuscript: CV, HGZ, SG, JMK, and BL. CV takes responsibility for the integrity of the data analysis.

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