

Association of Intact Parathyroid Hormone Levels with Subsequent Hip BMD Loss: The Osteoporotic Fractures in Men (MrOS) Study

Jeffrey R. Curtis, Susan K. Ewing, Douglas C. Bauer, Jane A. Cauley, Peggy M. Cawthon, Elizabeth Barrett-Connor, Elizabeth M. Haney, Areef Ishani, Serge Cremers, and Eric Orwoll

Department of Medicine, Division of Clinical Immunology/Rheumatology (J.R.C.), University of Alabama at Birmingham, Birmingham, Alabama 35294; Department of Medicine, Epidemiology and Biostatistics (S.K.E., D.C.B.), University of California, San Francisco, San Francisco, California 94143; Department of Epidemiology (J.A.C.) University of Pittsburgh, Pittsburgh, Pennsylvania 15261; San Francisco Coordinating Center (P.M.C.), California Pacific Medical Center, San Francisco, California 94107; Division of Epidemiology (E.B.-C.), Department of Family and Preventive Medicine, University of California, San Diego, California 92093; Department of Medicine (E.M.H.), and Bone and Mineral Unit (E.O.), Oregon Health and Science University, Portland, Oregon 97239; Department of Medicine (A.I.), University of Minnesota, Minneapolis, Minnesota 55404; and Department of Medicine, Endocrinology (S.O.), Columbia University, New York, New York 10032

Introduction: There is little information on the association between intact PTH (iPTH) and longitudinal changes in bone mineral density (BMD) in older men. This association was evaluated in relation to conditions related to higher iPTH [e.g. decreased renal function, low serum 25-hydroxyvitamin D (25[OH]D)].

Methods: Eligible men were part of a random sample of 1593 community-dwelling individuals aged 65 yr or older participating in the Osteoporotic Fractures in Men study with baseline iPTH data. Of these, 1227 had at least two BMD measurements at the total hip and femoral neck over a mean follow-up of 4.5 yr. Annualized BMD change across iPTH quartiles was estimated using mixed-effects regression models, adjusting for age, serum calcium, serum 25(OH)D, estimated glomerular filtration rate, and other factors. Splines were used to identify more optimal iPTH thresholds associated with less BMD loss.

Results: Among the cohort of 1138 eligible men, men in the highest quartile of iPTH (≥ 38 pg/ml) lost 0.46% per year at the total hip compared with men in the lowest iPTH quartile who lost 0.22% per year ($P = 0.0004$). Results were similar at the femoral neck. The association between iPTH and BMD loss was not modified by baseline estimated glomerular filtration rate or 25(OH)D status. Spline results suggested that iPTH levels below 30 pg/ml were more physiologically optimal than higher iPTH values in reducing BMD loss, although an exact threshold for optimal iPTH was not identified.

Conclusion: Older men with higher iPTH levels had approximately a 2-fold greater rate of BMD loss compared with men with lower iPTH levels, irrespective of estimated glomerular filtration rate and 25(OH)D. (*J Clin Endocrinol Metab* 97: 1937–1944, 2012)

Low levels of circulating serum 25-hydroxyvitamin D [25(OH)D] vitamin D have been previously shown to be associated with a greater rate of bone loss of the hip in older men (1). Although this effect may be in part mediated

through concomitant secondary hyperparathyroidism (2), the independent effect of higher PTH levels is unclear. Other factors, such as chronic kidney disease, are also associated with higher PTH levels, particularly if the glo-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

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doi: 10.1210/jc.2011-2431 Received August 29, 2011. Accepted February 22, 2012.

First Published Online March 22, 2012

Abbreviations: BMD, Bone mineral density; CV, coefficient of variation; DXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; iPTH, intact PTH; -2LL, -2 log likelihood; MrOS, Osteoporotic Fractures in Men; 25(OH)D, 25-hydroxyvitamin D.

merular filtration rate falls below 60 ml/min per 1.73 m² (3). Most prior research examining the effect of PTH on bone loss has been conducted in patients with compromised renal function (3, 4). Indeed, very few studies have examined the longitudinal association between PTH and bone mineral density (BMD) loss in community-dwelling individuals, men, and those with relatively normal renal function.

To test the hypothesis that increasing intact PTH level (iPTH) is associated with greater rates of bone loss at the hip in older, community-dwelling men, this association was evaluated in a randomly selected subcohort of men participating in the Osteoporotic Fractures in Men (MrOS) study. This association was also examined to evaluate whether it varied by renal function, serum 25(OH)D, and race/ethnicity.

Materials and Methods

Participants

MrOS recruited 5995 men from 2000 to 2002 who were at least 65 yr of age to evaluate osteoporosis, fractures, and healthy aging (5, 6). Men were not eligible to participate in MrOS if they had a history of bilateral hip replacement or an inability to walk without another person's assistance. Written informed consent was obtained from each participant, and the institutional review boards at each center approved the study protocol.

For this analysis, a sample of 1594 men was randomly selected to have iPTH and 25(OH)D measured at baseline. Of these individuals, 1227 (77%) had iPTH and 25(OH)D measurements and also had BMD measured at least twice, at baseline and at least one follow-up visit. Men receiving prescription osteoporosis medications such as bisphosphonates (n = 21), and those missing medication data at baseline (n = 68) were excluded from this analysis. Thus, 1138 men comprised the eligible sample for this analysis.

Measurement of iPTH, 25(OH)D, calcium, and renal function

Fasting morning blood was collected from each participant at baseline; serum was immediately processed after phlebotomy and stored at –70 C. All samples remained frozen until assay. Measurement of iPTH in serum was performed in duplicate using a Scantibodies immunoradiometric assay (Santee, CA) at Columbia University [normal range in serum defined by MrOS data set, 10–46 pg/ml; laboratory normal in EDTA plasma 10–66 pg/ml (7)]. Results of duplicate measures were averaged. Duplicate pooled serum controls were included in every other assay run. Using the pooled serum, the interassay coefficient of variation (CV) was 8.4%, and the intraassay CV was 5.7%. Measures for 25 dihydroxyvitamin D₂ (derived from ergocalciferol) and 25 dihydroxyvitamin D₃ (derived from cholecalciferol) were performed at the Mayo Clinic (Rochester, MN) using mass spectrometry as previously described (1), with an interassay coefficient of variation (CV) of 4.4% and an intraassay CV of 4.9%. Serum calcium was run on a COBAS Integra 800 automated analyzer (Roche

Diagnostics, Indianapolis, IN) and had a CV of 2.6%. Serum creatinine was measured using a variation of the Jaffe enzymatic method, with an interassay CV of 5.3%. Renal function was available for 1077 of the 1138 men and was expressed as estimated glomerular filtration rate (eGFR) in milliliter per minute per 1.73 m² using a standardized serum creatinine-based formula (8) normalized to a body surface area of 1.73 m².

Measurement of BMD

Men included in this analysis had total hip and femoral neck BMD measured at baseline and at least one follow-up visit. The follow-up visits included the MrOS Sleep study visit, an ancillary study visit to MrOS that was an average of 3.4 yr after baseline and provided additional BMD data, and the MrOS visit 2, an average of 4.5 yr after baseline.

BMD of the total hip and femoral neck was measured using fan beam dual-energy x-ray absorptiometry (DXA) (QDR 4500 W; Hologic Inc., Bedford, MA). At baseline, a hip phantom was circulated and measured at the six clinical sites. The difference between any two scanners was small, and the largest difference was 2.2% of the mean value. The interscanner CV was 0.9%, within acceptable limits for the hip phantom. To adjust for interclinic differences, statistical models included indicator variables for the individual scanners. Centralized quality control procedures, certification of DXA operators, and standardized procedures for scanning were used to ensure reproducibility of DXA measurements. Each clinic scanned a hip phantom throughout the study to monitor longitudinal changes in measures of bone density and content, and correction factors were applied to participant data as appropriate. The precision of DXA scans of the hip was 1–2% (9).

Clinical evaluation

At the baseline examination, MrOS participants completed a questionnaire that asked about age, race/ethnicity, comorbidities, smoking status, and alcohol use. Participants were asked to bring all current medications with them to the clinic. All prescription medications were recorded by the clinics, and data were stored in an electronic medications inventory database (San Francisco Coordinating Center, San Francisco, CA). Each medication was matched to its ingredient(s) based on the *Iowa Drug Information Service Drug Vocabulary* (College of Pharmacy, University of Iowa, Iowa City, IA) (10). Physical activity was assessed using the Physical Activity Scale for the Elderly (11, 12). Height (centimeters) was measured on Harpenden stadiometers and weight (kilograms) on standard balance beam or digital scales using standard protocols, with participants wearing light clothing without shoes. Body mass index was calculated as kilograms per square meter. Weight change was calculated by subtracting baseline weight from the follow-up weight. Grip strength (kilograms) was measured with a Jamar dynamometer (Hatfield, PA). Participants completed two trials for each hand, and the average of the four trials was used for analyses.

Statistical analysis

Characteristics of participants at the baseline examination were examined using χ^2 tests for categorical variables and ANOVA or Kruskal-Wallis tests for continuous variables. There is no well-accepted, physiologically normal value for iPTH, so iPTH was grouped into quartiles. Results were also evaluated in

light of a commonly used laboratory normal range for iPTH of less than 65 pg/ml (http://www.questdiagnostics.com/hcp/intguide/jsp/showintguidepage.jsp?fn=PTH_Intact.htm).

Random-effects regression models were used to examine the association between baseline iPTH quartiles and subsequent BMD loss at the total hip. Random effects models account for between-subject variation and within-subject correlations between repeated bone measurements. Our models allow each participant to have a unique intercept (baseline BMD level) and slope (change in BMD). Model coefficients were estimated using the restricted maximum likelihood method. Time was modeled as a continuous covariate, measured as the number of years from the baseline to follow-up BMD measurements. Fixed effects in the partially adjusted models included age, study site, weight at baseline, and weight change since baseline. Fixed effects in the fully adjusted models included those from the partially adjusted models as well as potential confounders that were hypothesized *a priori* to be associated with rate of change in hip BMD and iPTH and were found to be significant at a $P \leq 0.10$ [history of cardiovascular disease, history of hypertension, use of loop diuretics, season of blood draw, serum 25(OH) vitamin D, and eGFR] and other characteristics deemed clinically important (white race and serum calcium). Change in BMD is reported as annualized percent change, and the P value for trend across the iPTH quartiles was determined.

Restricted cubic splines were used to determine whether the relationship between iPTH and change in BMD was nonlinear and ascertain whether there might be a threshold value for iPTH (14, 15). Knots were placed at the fifth, 27.5th, 50th, 72.5th, and 95th percentiles of centered iPTH and calculated three cubic terms for each participant. To fit the spline and determine whether iPTH was associated with BMD loss, interactions of each of the cubic spline predictors with time as well as the individual cubic spline terms were entered in the partially adjusted and fully adjusted mixed models. The -2 log likelihood ($-2LL$) for this model was compared with the $-2LL$ for the nested model without the interactions between the spline terms and time. Differences in $-2LL$ were compared against a χ^2 with 3 degrees of freedom to determine whether the spline fit was significantly better than the linear fit. If the difference in the $-2LL$ was significant, the spline curve for BMD loss *vs.* iPTH was plotted to determine whether it suggested an iPTH threshold for BMD loss. Nonlinear mixed models were used to determine the precise value of this threshold; the $-2LL$ for this model was compared with the $-2LL$ for the linear model to determine whether the threshold model fit the data significantly better.

Because associations between iPTH and rate of change in hip BMD might be modified by eGFR, 25(OH)D, or race/ethnicity (non-Hispanic white *vs.* other), mixed models were run testing three-way interaction terms between each of these factors, iPTH quartiles, and time. For ease of interpretation, stratified results for these three factors are presented. eGFR was dichotomized at (<60 *vs.* ≥ 60 cc/min per 1.73 m 2). 25(OH)D was categorized as 20 ng/ml or less, between 20 and 30 ng/ml, and 30 ng/ml or greater (3). A sensitivity analysis was conducted which excluded all men with iPTH values greater than 65 pg/ml (3% of observations). All analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC).

Results

Characteristics of the cohort of 1138 men eligible for this analysis are shown in Table 1, stratified by quartile of iPTH. The median (interquartile range) value of iPTH was 29.2 (23.3, 37.7) pg/ml, with a minimum of 7.5 pg/ml and maximum of 802.5 pg/ml. Men in the highest quartile of iPTH (≥ 38 pg/ml) were older, experienced more weight loss, and had a higher prevalence of cardiovascular disease compared with men in other quartiles. Men in the highest iPTH quartile were more likely to use loop diuretics than those in other quartiles. Among the men in this quartile, 29% had eGFR less than 60 ml/min per 1.73 m 2 , and 36% had 25(OH)D levels 20 ng/ml or less. A number of other characteristics were also significantly different across quartiles, although the magnitude of difference for most remaining characteristics was small.

After adjustment for age, study site, race, weight change over the study period, history of cardiovascular disease, history of hypertension, use of loop diuretics, season of blood draw, serum calcium, serum 25(OH)D, and eGFR, the rate of BMD loss at both the total hip and the femoral neck was higher for each increasing iPTH quartile (Table 2). The greatest magnitude of change was observed among men in the highest quartile of iPTH; men in this quartile lost almost 0.5% per year at both the total hip and femoral neck, a rate twice as great as those in the lowest quartile of PTH levels. Tests for linear trend across the iPTH quartiles were significant in both the partially adjusted and fully adjusted models. Results that excluded the 3% of men with iPTH 65 pg/ml or greater in the highest iPTH quartile were minimally different; the multivariable-adjusted rate of BMD loss at the total hip and femoral neck among men in the highest quartile of iPTH was -0.42% per year and -0.48% per year, respectively (corresponding P trend values were 0.001 and 0.009). Substitution of body surface area-adjusted eGFR for eGFR did not alter these results (not shown).

Figure 1, A and B, displays the spline curves for change in total hip BMD and change in femoral neck BMD *vs.* baseline iPTH. Although the spline curve suggested that the rate of total hip BMD loss increased in men with iPTH values from 23 pg/ml (25th percentile) to 43 pg/ml (84th percentile), with no further increase in the rate of BMD loss thereafter, the nonlinear mixed model did not support a threshold effect in the dependence of the rate of change of total hip BMD on iPTH. The spline curve for femoral neck BMD loss was similar, with the rate of BMD loss increasing in men with iPTH between 28 and 43 pg/ml. The threshold suggested by the nonlinear mixed model was iPTH of 60 pg/ml, but this model was not significantly better than the linear model. This same iPTH threshold of

TABLE 1. Characteristics of MrOS participants by quartile of iPTH

Variable	Baseline total iPTH				P value
	Quartile 1 (<23 pg/ml) (n = 284)	Quartile 2 (23–29 pg/ml) (n = 285)	Quartile 3 (29–38 pg/ml) (n = 284)	Quartile 4 (≥38 pg/ml) (n = 285)	
Age (yr)	72.7 ± 5.4	72.2 ± 5.1	72.8 ± 5.5	74.1 ± 6.1	0.0002
Race/ethnicity					0.20
Caucasian	265 (93.3)	259 (90.9)	248 (87.3)	255 (89.5)	
African-American	6 (2.1)	7 (2.5)	12 (4.2)	11 (3.9)	
Asian	8 (2.8)	10 (3.5)	10 (3.5)	8 (2.8)	
Hispanic	2 (0.7)	3 (1.1)	11 (3.9)	9 (3.2)	
Other	3 (1.1)	6 (2.1)	3 (1.1)	2 (0.7)	
Change in weight (V1-V2) (%/yr)	−0.2 ± 1.1	−0.2 ± 1.1	−0.5 ± 1.2	−0.6 ± 1.2	0.0002
BMI (kg/m ²)	27.0 ± 3.4	27.5 ± 3.8	27.6 ± 3.7	28.0 ± 4.0	0.0236
BMD (g/cm ²)					
Total hip	0.98 ± 0.12	0.95 ± 0.13	0.96 ± 0.14	0.96 ± 0.14	0.09
Femoral neck	0.80 ± 0.12	0.78 ± 0.12	0.79 ± 0.13	0.78 ± 0.12	0.07
Total PASE score	156.3 ± 71.5	156.2 ± 64.9	151.5 ± 70.9	143.7 ± 66.3	0.0967
History of hypertension	118 (41.6)	103 (36.1)	129 (45.4)	144 (50.5)	0.0049
History of cardiovascular disease	44 (15.5)	48 (16.8)	60 (21.1)	68 (23.9)	0.0430
History of diabetes	39 (14.4)	39 (14.2)	29 (10.8)	45 (16.8)	0.26
Current thiazide diuretic use	41 (14.4)	37 (13.0)	32 (11.3)	46 (16.1)	0.38
Current loop diuretic use	6 (2.1)	7 (2.5)	9 (3.2)	23 (8.1)	0.0006
Current smoker	9 (3.2)	10 (3.5)	11 (3.9)	6 (2.1)	0.65
Alcohol use (drinks/wk)	5.1 ± 8.2	4.6 ± 7.0	5.3 ± 8.4	3.8 ± 6.3	0.16
Average grip strength (kg)	39.5 ± 7.5	39.7 ± 7.2	39.4 ± 8.0	39.0 ± 7.7	0.78
Serum creatinine (mg/dl)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 0.3	<0.0001
Serum calcium (mg/dl)	9.4 ± 0.3	9.3 ± 0.3	9.3 ± 0.4	9.3 ± 0.5	<0.0001
eGFR (ml/min per 1.73 m ²)	78.1 ± 14.9	80.5 ± 16.7	78.1 ± 16.5	71.9 ± 19.6	<0.0001
eGFR <60 ml/min per 1.73 m ²	35 (13.0)	24 (8.8)	32 (12.0)	77 (28.8)	<0.0001
Total 25(OH)D (ng/ml)	28.1 ± 8.0	26.0 ± 7.5	24.7 ± 7.1	23.3 ± 8.3	<0.0001
25(OH)D ≤20 ng/ml	44 (15.5)	57 (20.0)	68 (23.9)	103 (36.1)	<0.0001
25(OH)D 20–30 ng/ml	135 (47.5)	152 (53.3)	156 (54.9)	129 (45.3)	
25(OH)D ≥30 ng/ml	105 (37.0)	76 (26.7)	60 (21.1)	53 (18.6)	

Data for continuous variables are shown as mean ± SD and for categorical variables as n (%). BMI, Body mass index; PASE, Physical Activity Scale for the Elderly.

60 pg/ml was observed, even after excluding the 3% of outliers.

Stratified analyses that describe the fully adjusted association between iPTH and total hip BMD loss for men with eGFR above and below 60 ml/min per 1.73 m² are shown in Fig. 2. The rate of BMD loss was higher among men with reduced renal function compared with those

with normal renal function, and men in the highest iPTH quartile lost approximately twice the amount of BMD as men in the lowest quartile, irrespective of whether they had normal or low eGFR. Trend tests across iPTH quartiles for men with eGFR greater than 60 ml/min per 1.73 m² was significant ($P = 0.003$) but was borderline for the smaller number of men with eGFR less than 60 ml/min per

TABLE 2. Mean annualized percentage change in total hip and femoral neck BMD, by quartile of iPTH

Adjusted change in hip BMD (%/yr)	Quartiles of iPTH				Adjusted P for trend
	Q1 (<23 pg/ml)	Q2 (23–29 pg/ml)	Q3 (29–38 pg/ml)	Q4 (≥38 pg/ml)	
Total hip					
Partially adjusted ^a	−0.22 (−0.47, 0.00)	−0.26 (−0.52, −0.03)	−0.36 (−0.62, −0.12)	−0.49 (−0.60, −0.39)	0.0001
Fully adjusted ^b	−0.22 (−0.47, −0.00)	−0.24 (−0.49, −0.01)	−0.34 (−0.60, −0.11)	−0.46 (−0.58, −0.36)	0.0001
Femoral neck					
Partially adjusted ^a	−0.27 (−0.61, 0.05)	−0.19 (−0.55, 0.13)	−0.37 (−0.73, −0.04)	−0.53 (−0.68, −0.38)	0.003
Fully adjusted ^b	−0.26 (−0.58, 0.03)	−0.17 (−0.50, 0.12)	−0.31 (−0.65, −0.01)	−0.49 (−0.64, −0.35)	0.005

^a Adjusted for age, study site, and weight change over the study period.

^b Adjusted for age, study site, white race, weight change over the study period, history of cardiovascular disease, history of hypertension, use of loop diuretics, season of blood draw, serum calcium, serum 25(OH)D, and eGFR.

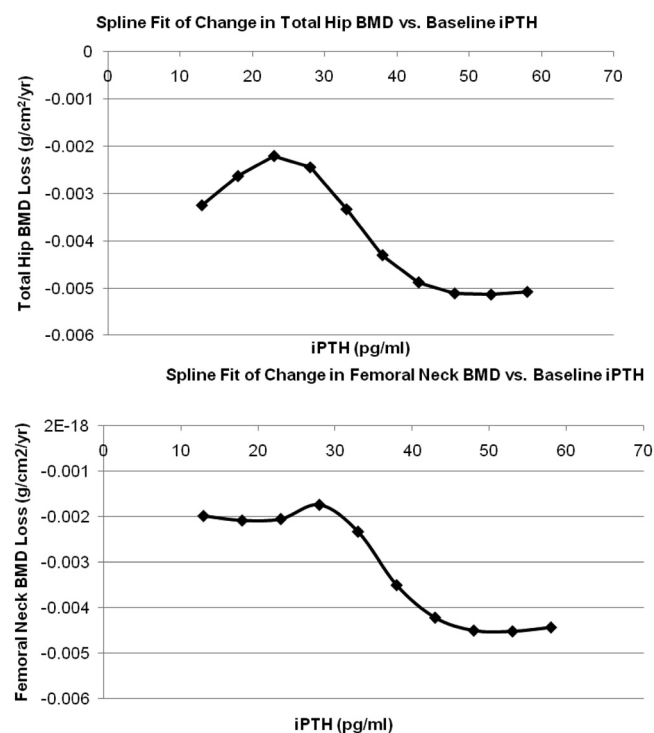


FIG. 1. Adjusted association between iPTH and total hip (A) and femoral neck (B) BMD loss. *, Values were adjusted for age, study site, white race, weight change over the study period, history of cardiovascular disease, history of hypertension, use of loop diuretics, season of blood draw, serum calcium, serum 25(OH)D, and eGFR.

1.73 m² ($P = 0.07$). The P value for interaction between eGFR less than 60 ml/min per 1.73 m² and iPTH quartiles was borderline significant at 0.13.

Stratified results across iPTH quartiles in three categories of 25(OH)D are shown in Fig. 3. Similar to the non-stratified results, the decline in BMD among men in the

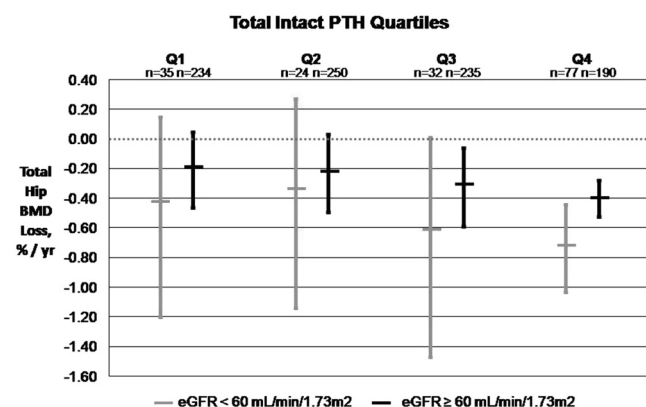


FIG. 2. Adjusted* association between baseline total intact PTH and total hip BMD loss, stratified by eGFR. Numbers in the bars reflect the number of men contributing to the analysis. Vertical bars denote the 95% confidence intervals. P value for interaction between pth quartile (Q) and eGFR = 0.13. *, Values were adjusted for age, study site, white race, weight change over the study period, history of cardiovascular disease, history of hypertension, use of loop diuretics, season of blood draw, serum calcium, and serum 25(OH)D. eGFR = estimated Glomerular Filtration Rate.

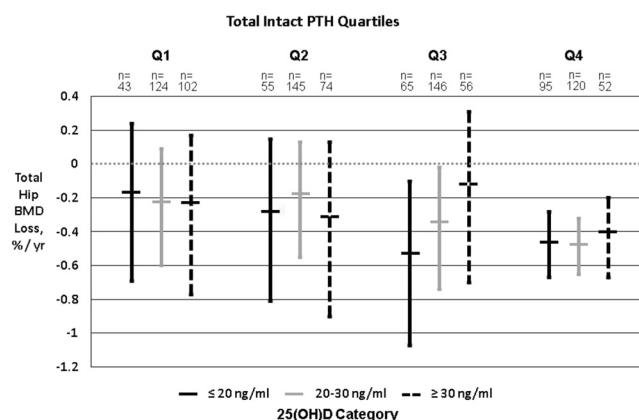


FIG. 3. Adjusted* Association between Baseline Total Intact PTH and Total Hip BMD Loss, Stratified by 25(OH)D. Numbers above the figure reflect the number of men contributing to the analysis. Vertical bars denote the 95% confidence intervals. P value for interaction between pth quartile (Q) and 25(OH)D = 0.34. *, Values were adjusted for age, study site, white race, weight change over the study period, history of cardiovascular disease, history of hypertension, use of loop diuretics, season of blood draw, serum calcium, and eGFR.

highest quartile of iPTH was approximately 2-fold greater compared with the lowest quartile of iPTH, irrespective of 25(OH)D level. In general, BMD loss increased with increasing iPTH quartile within each 25(OH)D group, although the trend was not as robust as in the unstratified analyses (P trend = 0.02 for 25(OH)D ≤ 20 ng/ml, P trend = 0.005 for 25(OH)D 20–30 ng/ml, and P trend = 0.50 for 25(OH)D ≥ 30 ng/ml). The P value for interaction between iPTH quartiles and 25(OH)D was not significant ($P = 0.34$).

Analyses stratified by race/ethnicity (not shown) revealed that the fully adjusted association between iPTH quartile and BMD loss was significant for Caucasian men (P trend = 0.0002 for total hip BMD loss and P trend = 0.007 for femoral neck BMD loss). This association among the small number of men ($n = 111$) who were not non-Hispanic Caucasians was not significant (P trend = 0.47 for total hip BMD loss or P trend = 0.50 for femoral neck BMD loss). BMD loss did not increase across the iPTH quartiles within the non-Caucasians as it did for the Caucasians.

Discussion

In this cohort of community-dwelling older men, a significant and independent association between higher levels of iPTH and decreasing total hip and femoral neck BMD was found over a mean follow-up of 4.5 yr. After multivariable adjustment, the rate of loss at the total hip among men in the highest quartile of iPTH was approximately 0.5% per year and was similar in magnitude to the rate of change at the femoral neck. The substantial majority of men (ap-

proximately 88%) with iPTH values in this highest quartile had values less than 65 pg/ml, a commonly used cut point for defining the normal reference range (in plasma). The spline analyses indicated that total hip BMD loss increased for iPTH levels between 23 and 43 pg/ml and femoral neck BMD loss increased for iPTH levels between 28 and 43 pg/ml, suggesting the possibility that an iPTH level less than 30 pg/ml is more physiologically optimal than higher values. However, the nonlinear mixed models did not support a threshold effect in the dependence of rate of change of total hip or femoral neck BMD on iPTH, although the models were likely underpowered to detect such a threshold with few men in the upper ranges of iPTH.

Results from the stratified analyses of renal function and 25(OH)D show the same general association between iPTH and BMD loss as in the unstratified analyses; men in the highest iPTH quartile had approximately twice the rate of BMD loss at the total hip compared with men at the lowest quartile, regardless of eGFR or 25(OH)D levels. The effect on the rate of BMD loss appeared to be much more affected by whether men were in higher quartiles of iPTH than their 25(OH)D category. Indeed, the difference in BMD loss between iPTH quartiles was much greater than the difference in BMD loss between 25(OH)D categories within a iPTH quartile. This is consistent with the hypothesis that the effect of low 25OHD on BMD loss is largely mediated through secondary hyperparathyroidism.

Only a few studies have examined associations with iPTH and BMD in men, and most were cross-sectional. The study, a prospective cohort study of osteoporosis and its determinants, evaluated 881 men in France (16). Among the 595 men aged 55–85 yr, the partial correlation coefficient between PTH and total hip BMD was -0.14 and was significant ($P < 0.005$). A weaker association that was not significant was observed at the femoral neck. A cross-sectional study of 419 Caucasian men in Rancho Bernardo, CA, found a modest inverse association between serum PTH and hip but not spine BMD (17). A Norwegian study that included 1442 men (18) found a significant cross-sectional association between increasing iPTH and lower total hip BMD but did not find a significant association at either the distal or ultradistal forearm. In general, these data suggest that the physiological effect of PTH is more important at sites with a higher cortical bone content such as the total hip. Future MrOS analyses that examine the association between iPTH and BMD changes at other sites (*e.g.* one third radius, lumbar spine) may further clarify the underlying biology at sites other than the hip.

The clinical significance of the magnitude of observed BMD loss deserves mention. Although in a clinical environment with an average least significant change limitation, it would take years to confidently measure these losses in an individual subject, it nevertheless should not diminish the importance of the finding that in the general population, PTH seems to be an important driver of BMD loss in men. Additionally, the rate of BMD loss has been shown to be an important and independent predictor of fractures. As a noted limitation, the follow-up period was a mean of only 4.5 yr; it is not known whether the men undergoing rapid bone loss in the prior or subsequent 4 or 5 yr would be the same individuals as those in the current analysis.

Longitudinal studies of men evaluating iPTH and BMD are scant. A longitudinal Canadian study of 191 men and 444 women older than 50 yr evaluated BMD change over 5 yr in relation to estimated creatinine clearance and iPTH (19). Although these investigators did observe a relationship between lower creatinine clearance and greater BMD loss, similar to what was found in our stratified analyses, they found no association between serum PTH and BMD change at either the hip or spine.

Although the analyses stratified by race/ethnicity were likely underpowered, these results suggested the possibility that the effect of iPTH on BMD loss is different in Caucasians than for non-Caucasians, with Caucasians having greater BMD loss for higher values of iPTH but with no clear trend in the non-Caucasians. Although comparative longitudinal data for non-Caucasians are limited, these results are supported by a large cross-sectional study of 1114 men between 30 and 79 yr of age that found some differences in the race- and ethnic group-specific association between PTH and BMD (20). The MrOS non-Caucasian group consisted of a mix of race/ethnicities, and certain groups may have a different skeletal response than others. Focusing on African-Americans in particular, in a cross-sectional study of 86 men in Boston with PTH and heel BMD measured in the winter, Black but not white men with elevated PTH had lower heel BMD compared with men with more normal PTH levels (21). Other small studies suggest, however, that African-American men are relatively resistant to the effects of secondary hyperparathyroidism when related to low vitamin D (22). The importance of this association is underscored by findings from multiple studies that have observed that low vitamin D levels are more prevalent in ethnic/racial groups with darker skin (13, 23).

Key strengths of our study include a large population of well-characterized, community-dwelling older men that had rigorous longitudinal assessment of serial BMD and excellent follow-up in association with carefully measured

laboratory data. This study is one of the largest analyses of the association between iPTH and rates of BMD loss in men and is one of the first longitudinal studies to evaluate the relation between bone loss and iPTH levels in men with normal or only mildly reduced kidney function. Also, multiple important covariates were adjusted for in the multivariable models that were also able to evaluate potential interactions between iPTH and renal function and 25(OH)D and to test for thresholds using cubic spline analyses.

Despite these strengths, these results must be interpreted in light of some limitations. Laboratory data were measured only at baseline, and changes in iPTH over time could not be evaluated or correlated with changes in BMD. Some of our subgroup analyses were based on relatively small numbers of persons, especially for stratified analyses, and interaction terms are often underpowered to detect effect modification. Finally, MrOS participants are likely healthier than general population, which could limit the generalizability of our findings.

In conclusion, higher levels of PTH, even within laboratory normal plasma reference ranges, were associated with considerably higher rates of hip BMD loss. This association was observed both among patients with normal and reduced renal function. The possibility to intervene, perhaps through more aggressive vitamin D treatment, to reduce iPTH levels into a more physiologically optimal range should be examined in clinical trials.

Acknowledgments

Address all correspondence and requests for reprints to: Jeffrey R Curtis, 510 20th Street South, Faculty Office Towers 805D, Birmingham Alabama 35294. E-mail: jcurtis@uab.edu.

This work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute on Aging, the National Center for Research Resources, and National Institutes of Health (NIH) Roadmap for Medical Research under Grants U01 AR45580, U01 AR45614, U01 AR45632, U01 AR45647, U01AR45654, U01 AR45583, U01 AG18197, U01-AG027810, and UL1 RR024140. J.R.C. is supported by NIH Grant AR 053351. E.M.H. is supported by NIH Grant AR051926. S.C. is supported by NIH Grants R01 Dk32333–25 and UL1RR024156. The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding.

Disclosure Summary: The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding. The following provide support: J.R.C., S.C., and E.M.H. are supported by the National Institutes of Health. All the other coauthors have nothing to disclose.

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