

Genetic Influence on Bone Turnover in Postmenopausal Twins*

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ABSTRACT

Postmenopausal bone mass is determined by both peak bone mass and subsequent bone loss. Previous studies have shown that peak bone mass is under genetic influence mediated partly by factors affecting bone formation. The rate of bone loss increases markedly after the menopause, but is highly variable from subject to subject. The aims of this study were to determine whether postmenopausal bone turnover was under genetic control, which should be linked to the genetic influence on the rate of postmenopausal bone loss. A classical twin study was performed that compared the intraclass correlations in monozygotic (MZ) twins with those in dizygotic (DZ) twins, with any difference assumed to be due to genetic factors. Markers of bone formation and resorption were measured in 240 untreated postmenopausal twins, aged 45–69 yr, on the average 12.3 yr (SD, 6.0) postmenopause, including 61 MZ pairs and 59 DZ pairs. The intraclass correlation coefficient of MZ twin pairs, rMZ (95% confidence interval), for 2 specific markers of bone formation, serum osteocalcin and bone-specific alkaline phosphatase, were higher than the corresponding rDZ [0.67 (range, 0.59–0.75) vs. 0.48 (range, 0.35–0.61); $P = 0.06$] for osteocalcin and 0.53 (range, 0.41–0.65) vs. 0.21 (range, 0.01–0.41;

$P = 0.02$) for bone-specific alkaline phosphatase]. For serum propeptide of type I collagen, a type I collagen synthesis marker that exhibits only a slight increase after menopause, a high proportion of its variance was explained by genetic factors [rMZ = 0.82 (0.77–0.87), rDZ = 0.33 (0.16–0.50); $P < 0.001$]. The correlations for bone resorption measured by three distinct urinary markers, total deoxypyridinoline and two cross-linked type I collagen peptides (CrossLaps and NTX), that increase markedly after menopause were higher in MZ than in DZ pairs, but the difference reached significance only for NTX ($P = 0.03$). For urinary free deoxypyridinoline, a marker reflecting bone collagen degradation that increases moderately after menopause, the proportion of the variance explained by genetic factors was highly significant ($P = 0.002$).

In conclusion, our data indicate that a proportion of the variance in postmenopausal levels of both bone formation and resorption markers are explained by genetic factors, but this contribution was clearly significant only for markers that do not change markedly at the menopause. These data suggest that the contribution of genetic factors to overall postmenopausal bone turnover and possibly bone loss is likely to be small. (*J Clin Endocrinol Metab* 81: 140–146, 1996)

LOW BONE MASS in osteoporosis depends on the peak bone mass achieved in the third and fourth decades and on the subsequent rate of loss (1, 2). Twin (3–6) and family (2, 7–9) studies have shown that a large proportion of the variance in peak bone mass is explained by genetic factors. Because bone mass is the result of the net balance between bone resorption and bone formation (bone remodeling), the genetic effect on bone mass accretion should be mediated through a genetic influence on bone remodeling.

Kelly *et al.* (6) have shown that a large proportion of the serum osteocalcin variance, a specific marker of bone formation, is explained by genetic factors in premenopausal twins and that this genetic effect is probably mediated through vitamin D receptor gene polymorphisms (10). More recently, similar findings have been found by Tokita *et al.* (11) for serum C propeptide of type I collagen (PICP), a marker of type I collagen synthesis that is the major protein of bone matrix. In addition, dizygotic (DZ) twin pairs differences in serum osteocalcin (6) and PICP (11) levels predict differences in lumbar spine and femoral neck bone mineral density

(BMD), suggesting that the genetic effect on bone formation is closely related to the genetic effect on peak BMD.

A genetic influence on bone resorption in premenopausal women has not been yet clearly demonstrated. Kelly *et al.* (6) were unable to demonstrate a genetic effect on the urinary excretion of hydroxyproline and calcium, two nonspecific markers of bone resorption. In contrast, Tokita *et al.* (11) recently reported that the genetic factors explained significantly the variance in the serum concentration of the pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP). Although serum ICTP appears to be correlated with collagen and bone resorption (12), it is not clear whether it reflects bone formation and/or bone resorption (13). Taken together, these findings suggest that genetic factors explain a large part of the overall rate of bone formation variance in premenopausal women, leading to a genetic influence on peak bone mass.

In contrast, the reasons for the large interindividual variability in the rate of postmenopausal bone loss (1, 14), which is the other component involved in the pathogenesis of osteoporosis, are less clear. As the precise evaluation of the rate of bone loss in a single patient requires repeated bone mass measurements over a long period, few studies have investigated the determinants of bone loss. Christian *et al.* (15) in a population of male twins studied over a 16-yr period found no significant genetic contributions to the change in radial bone mass despite evidence of genetic effects on bone mass

Received June 8, 1995. Revision received August 22, 1995. Accepted August 31, 1995.

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* This work was supported in part by a grant from the Wellcome Trust.

itself. Recently, in a population comprising male and female twins from 25–75 yr of age, Kelly *et al.* (16) suggested the existence of a genetic influence on the BMD changes at the spine and Ward's triangle, but were unable to demonstrate a significant effect at the femoral neck over a median 3-yr follow-up.

The rate of bone loss in postmenopausal women depends on the negative balance between resorption and formation, and some studies have shown that the rate of bone loss is highly correlated with the postmenopausal increase in bone turnover, *i.e.* that high turnover is associated with accelerated bone loss ("fast bone losers"). Such correlations have been found in prospective studies of bone mass measured repeatedly over 2–12 yr (1, 14, 17–19).

To determine whether a proportion of the variance in bone turnover in postmenopausal women is explained by genetic factors, we looked for a genetic influence on the levels of biochemical markers of bone turnover in a large group of MZ and DZ postmenopausal twins. For this purpose, we measured the most sensitive and specific markers of bone turnover (20), including direct immunoassays for serum bone-specific alkaline phosphatase (BAP) (21), human osteocalcin (OC) (22), and PICP for bone formation. To evaluate bone resorption, several studies have shown that the total excretion of pyridinoline (Pyr) and deoxypyridinoline (D-Pyr), two cross-links of the extracellular matrix of bone that are released in urine as both free and peptide-bound forms, are more specific and sensitive than resorption markers such as urinary hydroxyproline or calcium excretion (23–26). However, their assays by high performance liquid chromatography are quite cumbersome, and there is clearly a need for more convenient assays with improved precision. Recently, direct immunoassays have been developed, using antibodies that recognize free Pyr and free D-Pyr (27, 28), urinary type I collagen cross-linked peptide (NTX) (29), or type I collagen C-telopeptide breakdown products (CrossLaps) (30), and preliminary results indicate that these assays could represent an improvement over high performance liquid chromatography analysis of Pyr or D-Pyr (29, 30)

Subjects and Methods

Subjects

Two hundred and forty postmenopausal twins (median, 12 yr postmenopause; range, 2–41 yr), comprising 61 MZ and 59 DZ pairs, were studied. Twins were recruited from two sources: a national twin register and a media campaign. Twin zygosity was determined by multiplex DNA fingerprinting using variable number tandem repeats at multiple loci. None of the twins had a history of serious medical disease or was currently taking drugs known to affect bone metabolism, including postmenopausal estrogen therapy. Past hormonal replacement therapy users were included if use was more than 6 months previously (median duration, 9 months; 7 yr since stopping). Blood and urine samples were collected in the early morning after an overnight fast and stored at -20°C until assayed. All twin pair samples were measured in duplicate in the same assay.

Markers of bone turnover

Bone formation. Serum total OC was measured with a human-specific two-site immunoradiometric assay (ELSA-OSTEO, Cis Biointernational, Bagnols/Cèze, France) that recognizes a large N-terminal midfragment

in addition to the intact molecule (22). This fragment circulates *in vivo* and is also generated from the intact molecule during processing of blood samples. Thus, including the N-terminal midfragment in the assay of circulating OC allows for correction for potential degradation of the intact molecule and increases both the stability and the sensitivity of OC measurement (22, 31). The intra- and interassay coefficients of variation (CVs) are reported to be below 4% and 6%, respectively, and the sensitivity is 0.4 ng/mL (22).

Serum BAP was measured with a human-specific immunoradiometric assay using two monoclonal antibodies directed against the human bone isoenzyme and BAP purified from human SAOS-2 osteosarcoma cells as a standard (Ostase, Hybritech, San Diego, CA). This assay cross-reacts only 16% with the circulating liver isoenzyme. The sensitivity of the assay is 0.2 ng/mL, and the intra- and interassay CVs are less than 7% and 9%, respectively (21).

Serum PICP was measured with a two site enzyme-linked immunosorbent assay (ELISA) with uses a monoclonal and a polyclonal antibody raised against human PICP purified from skin fibroblast cultures (32). The sensitivity of the assay is 1 ng/mL, and the intra- and interassay CVs are below 7%.

Bone resorption. Urinary free D-Pyr was measured on nonhydrolyzed urine samples by an ELISA that uses a monoclonal antibody with less than 1% cross-reactivity with free Pyr (Pyrilinks-D, MetraBiosystem, Mountain View, CA) and no significant interaction with cross-linked peptides (28). The intra- and interassay CVs are less than 10% and 15%, respectively, and the detection limit is 3 nmol/L.

Urinary total D-Pyr was measured by the same ELISA used for free D-Pyr (see above), but after hydrolysis of the urine samples.

Urinary type I collagen cross-linked N-telopeptide (NTX) was measured by an ELISA (Osteomark, Ostex) (29) that uses a monoclonal antibody directed against the N-telopeptide to helix intermolecular cross-linking domain of type I collagen isolated from human urine. This monoclonal antibody does not recognize free cross-links (29). As the yield of immunoreactive NTX peptides per U human bone collagen on exhaustive collagenase digestion is highly reproducible (29), this assay is calibrated by the amount of bone collagen (bone collagen equivalent) from which peptides were generated by collagenase digestion. The intra- and interassay CVs are less than 10%, and the sensitivity is 25 nmol/L.

Urinary type I C-telopeptide breakdown products (CrossLaps) was measured by an ELISA (CrossLaps ELISA, Osteometer, Rodovre, Denmark) based on an immobilized synthetic peptide with an amino acid sequence specific for a part of the C-telopeptide of the α_1 -chain of type I collagen (Glu-Lys-Ala-His-Asp-Gly-Gly-Arg; CrossLaps antigen) (30). During incubation with an antibody raised to this sequence, competition takes place between the immobilized peptide and the breakdown products of the α_1 -chain of type I collagen in urine. This assay does not cross-react with free cross-links (30). The intra- and interassay CVs are less than 10% and 13%, respectively, and the detection limit is 0.5 $\mu\text{g/mL}$.

All urinary assays were performed on the second void urine sample, and the data were corrected by the urinary creatinine concentration measured by a standard colorimetric method.

Bone densitometry. Bone densitometry of the femoral neck and lumbar spine (L1–L4) was performed using Hologic QDR 2000 dual energy x-ray absorptiometer (Hologic, Waltham, MA). The reproducibility of this method in our hands in volunteers and patients has a CV of 0.6–1.6%.

Statistical analysis

The rationale for using a twin study to determine genetic influence lies in the comparison between MZ and DZ pairs. If MZ twins share a trait more closely than DZ twins, this is likely to be due to genetic factors, as MZ twins share the same genes, and DZ twins share, on the average, only 50% of their genes. The extent of genetic influence is, therefore, the difference between the correlations of a trait in MZ and DZ twin pairs, the major assumptions being that environmental influences on MZ and DZ twins are similar. The primary analysis is, therefore, the calculation of the within-pair correlations using the intraclass correlation coefficient (r) for MZ (r_{MZ}) and DZ (r_{DZ}) pairs. The intraclass correlation coefficients were calculated using ANOVA methods and a Fortran-based twin analysis program (TWINAN 90) (33). This program automatically rec-

ommends a Box-Cox transformation if normality is not met. The TWINAN 90 program can then be run again, carrying out these recommended transformations. The assumptions necessary for this twin analysis model were equal variance in MZ and DZ pairs, bivariate normality, no evidence of multiplicative gene interactions, and similar shared environments between MZ and DZ pairs. The first two assumptions are automatically tested in the twin program, and the third can be suspected from the results. Using the TWINAN 90 model, potential confounding factors, such as weight, height, age, smoking status, past estrogen replacement therapy, and years since menopause, can be examined by fitting them together with the markers in multiple regression. The individuals are then reentered, and the ANOVA results compared with the crude analysis.

Differences in bone marker levels between MZ and DZ pairs were tested by nonparametric Mann-Whitney test. Relationships between within-twin pair differences in bone marker levels and within-twin pair differences in lumbar spine and femoral neck BMD were performed by linear regression analysis.

Results

The MZ and DZ pairs were similar in terms of age (MZ, 61.2 ± 4.8 yr; DZ, 60.7 ± 5.6 yr), age at menopause (MZ, 48.1 ± 6.5 yr; DZ, 48.1 ± 6.2 yr), body mass index (MZ, 24 ± 3 kg/m²; DZ, 25 ± 5 kg/m²), proportion of ever smokers (MZ, 40%; DZ, 47%), ever use of the oral contraceptive pill (MZ, 25%; DZ, 36%), and estrogen replacement therapy (MZ, 14%; DZ, 19%). No statistically significant differences were seen for any of those characteristics between MZ and DZ groups. The mean levels of bone formation and bone resorption markers are shown in Table 1. There were no marked differences between the MZ and DZ groups for mean levels of the markers, and the ranges and variance were similar.

The rMZ for all bone formation markers was higher than the corresponding rDZ; the difference was greater for PICP (Table 2 and Fig. 1). For the bone resorption markers, rMZ was higher than rDZ for total D-Pyr and two cross-linked type I collagen peptides (CrossLaps and NTX); the difference reached significance only for NTX ($P = 0.03$). In contrast, for free D-Pyr, the proportion of the variance explained by genetic factors was highly significant (Table 2 and Fig. 2).

To examine the possible relationship between genetic effects on serum PICP and urinary excretion of free D-Pyr (the two bone markers for which the genetic contribution is highly significant), on the one hand, and BMD, on the other hand, we compared the within-twin (MZ and DZ) pair differences in both markers with the within-twin pair differences (Δ) in both lumbar spine and femoral neck BMD using linear regression. No significant correlations were observed between Δ PICP and Δ free D-Pyr and either Δ lumbar spine

BMD or Δ femoral neck BMD (Fig. 3). In addition, none of the Δ in other markers correlated with Δ BMD; the r^2 values ranged from 0.0003–0.026 ($P = 0.09$ to 0.9), except for NTX, for which Δ NTX correlated significantly with Δ lumbar spine BMD ($r^2 = 0.04$; $P = 0.03$) and with Δ femoral neck BMD ($r^2 = 0.08$; $P = 0.01$). These results were not significantly altered after adjusting for age (data not shown).

Discussion

A large proportion of peak BMD variance in young premenopausal women is explained by genetic factors (5). The acquisition of peak bone mass results from bone modeling during skeletal development and linear growth, whereas its maintenance in adults results from the coupling mechanism between the activities of bone formation and bone resorption. It seems likely that genetic effects on peak bone mass should be mediated by a genetic influence on bone turnover, especially on bone formation. Two studies have clearly shown that a large proportion of the variance in bone formation rate, assessed by serum osteocalcin, which is synthesized by osteoblasts (6), and serum PICP, reflecting the synthesis of type I collagen (11), is explained by genetic factors in populations comprising mainly young adults. In addition, recent findings suggest that the molecular basis of the genetic effect on osteocalcin levels could be related to vitamin D receptor polymorphisms (10), which has been suggested to explain up to 75% of the total genetic effect on peak bone mass (34). Although others have not confirmed these studies (35, 36), a recent study in postmenopausal twins in the United Kingdom has also shown a relationship between bone mass and vitamin D receptor gene polymorphisms (37). A further study has not shown any influence of these polymorphisms in rates of bone loss in postmenopausal women followed for a few years after the menopause (38).

After the menopause, bone mass results from both the peak bone mass and the rate of bone loss. The rate of bone loss in early postmenopausal women demonstrates a large heterogeneity between individuals, with about 25% of the women losing more than 3%/yr (14). In addition, a long term follow-up study from the same group suggests that women classified as rapid losers after the menopause still have an increased rate of bone loss after a 12-yr period, and they have lost 50% more bone than slow losers (1). The identification of factors responsible for this heterogeneity in the postmenopausal rate of bone loss is thus crucial for a comprehensive understanding of the pathogenesis of osteoporosis and the development of effective strategies of prevention.

Although postmenopausal bone loss is clearly due to a dramatic increase in bone turnover, with an excess of bone resorption resulting from the cessation of ovarian function, no study has been able to demonstrate a correlation between the postmenopausal rate of bone loss and residual estrogen levels. In this study we investigated the role of a potential genetic influence on postmenopausal bone turnover because we reasoned that if the rate of bone loss is under genetic influence, these should be mediated in part by an effect on postmenopausal bone turnover. To assess the genetic influence on postmenopausal bone turnover, we measured three

TABLE 1. Bone marker levels in MZ and DZ postmenopausal twins

Bone markers	MZ (n = 122)	DZ (n = 118)	P (MZ vs. DZ)
Bone formation			
OC (ng/mL)	24.0 ± 8.4	24.9 ± 9.7	0.65
BAP (ng/mL)	13.8 ± 4.8	14.3 ± 5.4	0.74
PICP (ng/mL)	91 ± 26	84 ± 28	0.08
Bone resorption			
Free D-Pyr (nmol/mmol Cr)	5.85 ± 1.48	5.64 ± 1.56	0.25
Total D-Pyr (nmol/mmol Cr)	12.4 ± 4.5	12.0 ± 4.2	0.26
Cross Laps (μ g/mmol Cr)	449 ± 223	409 ± 228	0.12
NTX (nmol/mmol Cr)	57.0 ± 26.1	55.1 ± 27.9	0.44

TABLE 2. Variances (mean squares) and intraclass correlation coefficients (r) for markers of bone turnover in postmenopausal MZ and DZ twins

	MZ (n = 61)			rMZ (95% CI)	DZ (n = 59)			rDZ (95% CI)	P (rMZ vs. rDZ)	Heritability estimates (95% CI) ^a
	Mean squares				Mean squares					
	Among	Within	Total		Among	Within	Total			
Bone formation										
OC	1.385	0.276	1.662	0.67 (0.59–0.75)	1.76	0.620	2.380	0.48 (0.35–0.61)	0.06	0.37 (–0.11–0.85)
EAP	1.548	0.473	2.021	0.53 (0.41–0.65)	1.228	0.802	2.030	0.21 (0.01–0.41)	0.02	0.64 (0.03–1.25)
PICP	1.570	0.156	1.726	0.82 (0.77–0.87)	1.520	0.775	2.295	0.33 (0.16–0.50)	<0.001	0.99 (0.51–1.47)
Bone resorption										
Free D-Pyr	1.717	0.416	2.132	0.61 (0.51–0.71)	1.136	0.791	1.927	0.18 (–0.03–0.39)	0.002	0.86 (0.27–1.45)
Total D-Pyr	1.719	0.492	2.211	0.56 (0.45–0.67)	1.257	0.578	1.836	0.37 (0.21–0.53)	0.10	0.37 (–0.20–0.94)
Cross Laps	1.504	0.372	1.875	0.60 (0.50–0.70)	1.533	0.642	2.175	0.41 (0.26–0.53)	0.08	0.39 (–0.15–0.93)
NTX	1.400	0.332	1.732	0.62 (0.52–0.72)	1.551	0.765	2.317	0.34 (0.17–0.51)	0.03	0.55 (–0.02–1.11)

^a Falconer's index of heritability calculated as 2 (rMZ – rDZ).

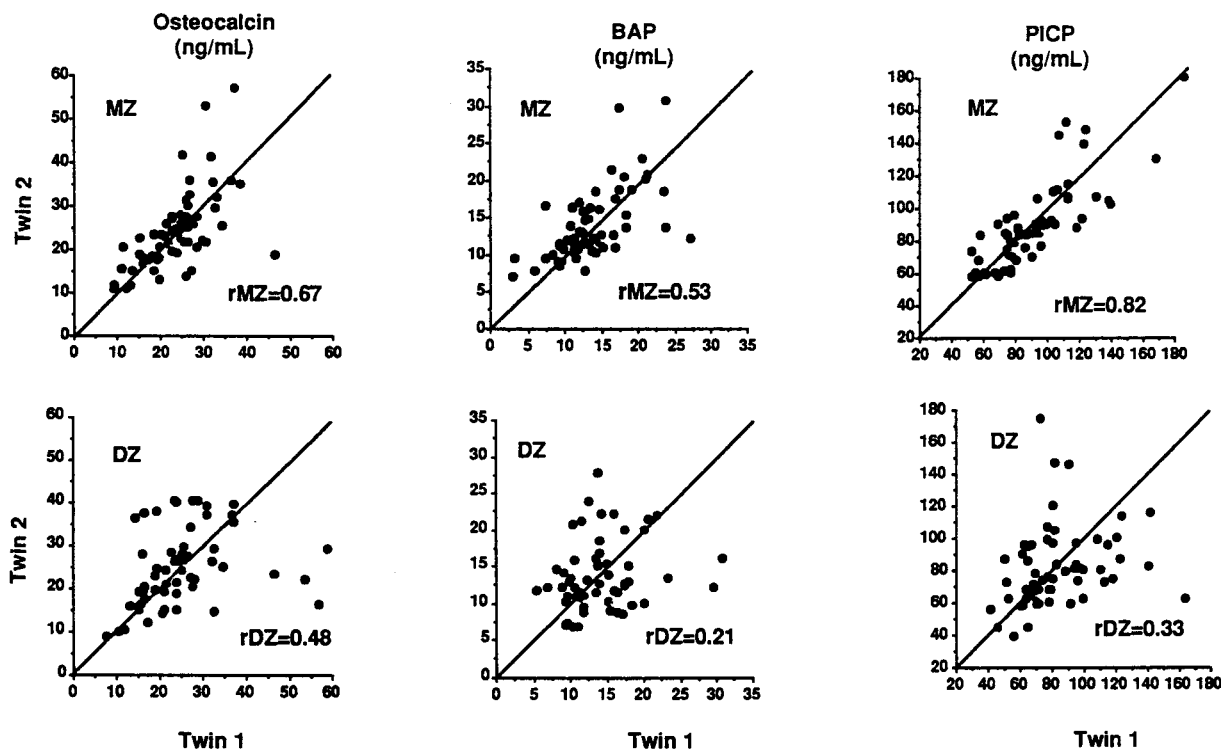


FIG. 1. Markers of bone formation in MZ and DZ postmenopausal twins. Within-twin pair (twin 2 vs. twin 1) correlations about the line of identity for serum OC, BAP, and PICP are shown.

markers of bone formation and four markers of bone resorption in a large group of MZ and DZ twin pairs, all untreated postmenopausal women. The twin analysis assumes that intrapair variance of MZ twins is due to environmental factors and measurement errors; intrapair variance in DZ twins is additionally due to genetic factors. It is also assumed that common environmental factors are shared to a similar extent between MZ and DZ twins. Therefore, when rMZ is significantly higher than rDZ, it indicates that genetic factors contribute to the variance in the analyzed trait.

Our data show that for all three markers of bone formation, i.e. OC, BAP, and PICP, that rMZ is higher than rDZ, suggesting that the bone formation rate in postmenopausal women is under genetic influence. However, the proportion of the variance explained by genetic factors was significant only for BAP and PICP. Menopause is associated with an

increase in bone formation and resorption, which has been well documented by histomorphometric data comparing normal women in their thirties with women in their late sixties (39). It has been shown that serum OC increases after the menopause and that it is closely correlated with histomorphometric parameters of bone formation in postmenopausal osteoporosis (40, 41). In addition, serum OC correlates with the spontaneous rate of bone loss assessed by repeated measurements of the bone mineral content of the radius and the lumbar spine (18). In contrast, PICP is poorly correlated with histomorphometric parameters of bone formation in osteoporotic women (42) and does not (43) or only slightly (44) increase after the menopause, and serum PICP is not correlated with the rate of bone loss measured by densitometry (42). The level of bone markers in a given postmenopausal woman results from both its premenopausal value

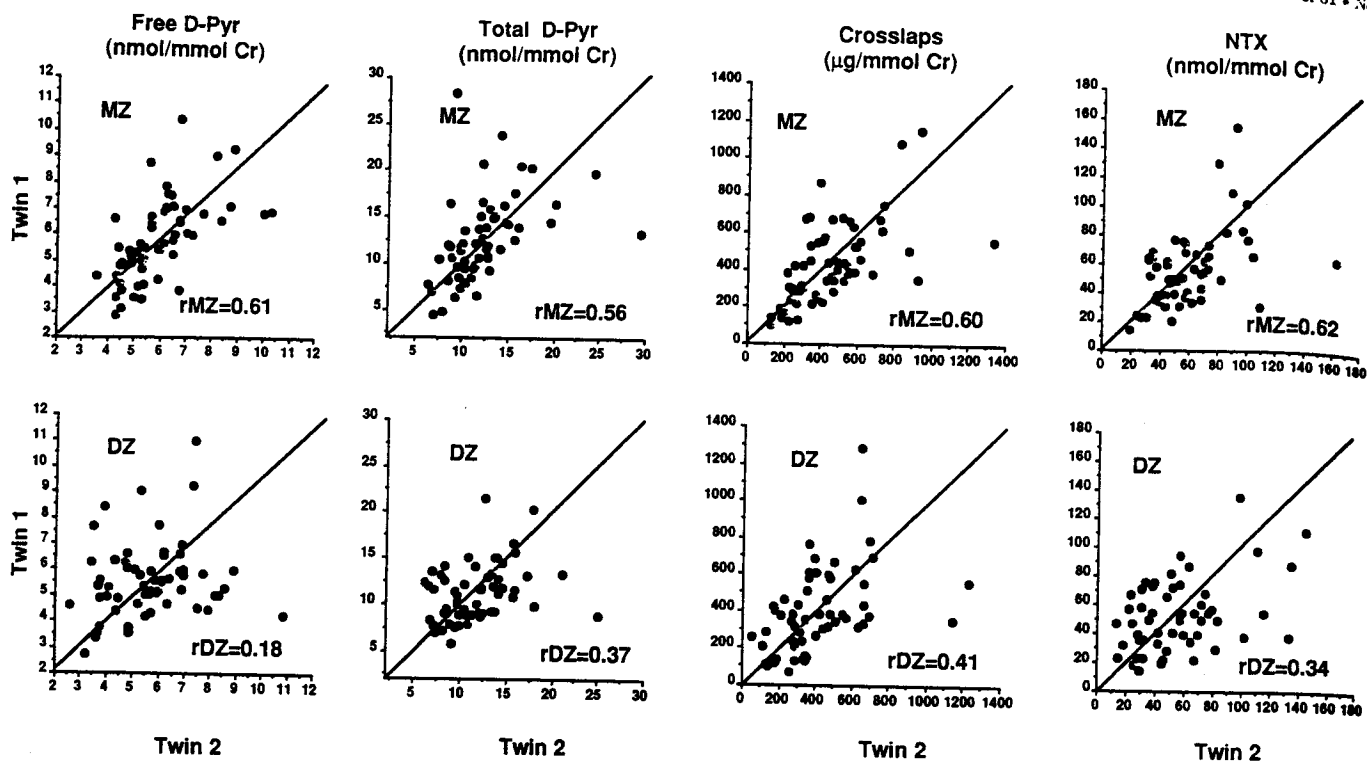


FIG. 2. Markers of bone resorption in MZ and DZ postmenopausal twins. Within-twin pair (twin 2 vs. twin 1) correlations about the line of identity for the urinary excretion of free D-Pyr, total D-Pyr, CrossLaps, and NTX are shown.

and its increase at the time of menopause. Thus, to investigate the genetic effect on postmenopausal bone turnover, a marker that markedly increases after the menopause, such as OC and BAP, is likely to be more useful than a marker that does not reflect the increased bone turnover rate, such as PICP. For OC, the difference between rMZ and rDZ found in our postmenopausal population was lower than that reported by Kelly *et al.* (6) in a group of twins comprising mainly premenopausal women (0.19 vs. 0.60), suggesting that although the premenopausal bone formation rate is under genetic influence, the postmenopausal increase in OC may not be. In contrast, as serum PICP levels do not or only slightly change at the time of menopause, the genetic influence found in premenopausal women (11) persists. There is little data with which to compare the genetic influence on BAP results.

Among the three specific and sensitive markers of bone resorption *i.e.* total D-Pyr, CrossLaps, and NTX, rMZ was significantly higher than rDZ only for NTX, suggesting that genetic factors are not a major determinant of bone resorption variance in postmenopausal women. However, given the precision error on urinary bone resorption marker measurements (from 25–30%) (43), our study may not have the power to detect small differences between rMZ and rDZ. Few data have been generated to date on the potential genetic influence on bone resorption. Kelly *et al.* (6) were also unable to show a genetic influence on the urinary excretion of hydroxyproline and calcium, but one could argue that these are nonspecific markers of bone resorption and, therefore, poorly sensitive. Recently, Tokita *et al.* (11) showed that genetic factors contribute to the variance in serum ICTP, a

pyridinoline cross-linked peptide. The significance of this marker, however, is unclear. Serum ICTP does not increase as expected after the menopause (13, 43), does not correlate with postmenopausal bone loss (13), and paradoxically increases after nandrolone decanoate therapy (13), an anabolic steroid that decreases bone resorption and increases bone formation. The urinary excretion of free D-Pyr differed from that of other bone resorption markers, as the difference between rMZ and rDZ was highly significant. However, the facts that the ratio of rMZ/rDZ far exceeded 2 and that rDZ was not significantly different from zero raise the possibility that interactions of a number of different genes were responsible for this effect, which would tend to overestimate the heritability value. The reasons for the discrepancy between free D-Pyr and the other bone resorption markers are unclear. However, we have recently shown that the urinary excretions of free and peptide-bound cross-links are differently affected by bisphosphonate and estrogen therapy (45). Estrogen treatment induced a similar decrease in free and peptide-bound cross-links, whereas bisphosphonate decreased only the peptide-bound forms, as measured with CrossLaps and NTX assays, suggesting that these two bone cross-link forms could reflect different aspects of bone collagen degradation (45).

It has been previously shown that within-twin pair differences in serum OC (6) and serum PICP (11) could predict differences in BMD at the lumbar spine and femoral neck in young adults, suggesting a relationship between the genetic effect on bone turnover rate and the genetic influence on BMD. In contrast, in this study, differences in neither PICP nor free D-Pyr, the two bone markers for which rMZ was

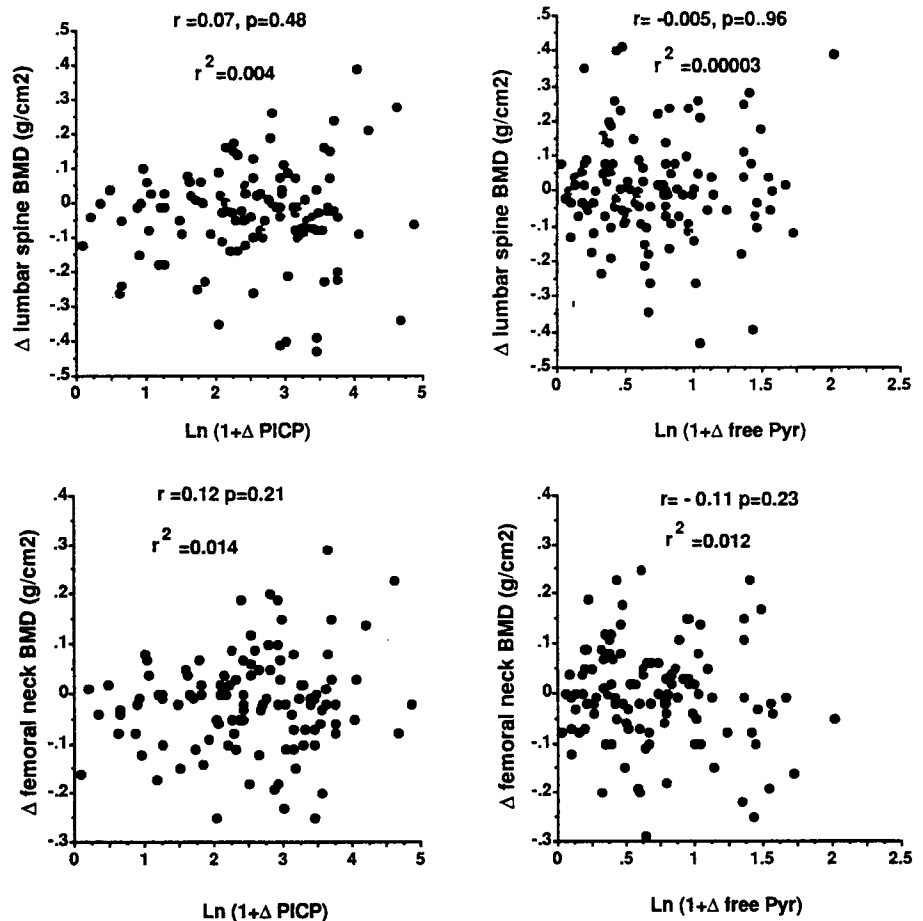


FIG. 3. Relationships between intrapair differences in MZ and DZ twins in serum PICP and urinary excretion of free D-Pyr, on the one hand, and intrapair differences in BMD at the lumbar spine and femoral neck, on the other hand.

highly significantly different from rDZ, were related to differences in BMD measured at both the lumbar spine and the femoral neck. These findings suggest that the significant genetic influence on these two biochemical markers, which reflect type I collagen turnover in various tissues, does not reflect postmenopausal changes in bone turnover and bone mass.

In conclusion, we have shown that genetic factors are probably not a major determinant in explaining the large interindividual variance in the levels of bone turnover markers in postmenopausal women. This suggests that, contrasting with the well documented genetic influence on premenopausal bone turnover and peak bone mass, environmental mechanisms are likely to play a large role in mediating postmenopausal bone turnover. As the increased bone turnover after menopause is likely to be responsible for the rate of bone loss, our data also suggest that genetic factors may not be a major determinant in explaining the variance in postmenopausal bone loss.

Acknowledgments

We thank J. Baker, K. Baan, O. Borel, N. Buyer, C. Chervet, C. Manzi, C. Richerd, and G. Surdelescu for excellent technical assistance, and Dr. C. Slemenda for helpful discussions.

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