

Genetic Influences on Type I Collagen Synthesis and Degradation: Further Evidence for Genetic Regulation of Bone Turnover*

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ABSTRACT

Circulating osteocalcin, a marker of bone formation, is under strong genetic influence, and this effect is related to the genetic influence on bone density. To examine genetic influences on bone turnover further, other markers of bone formation (serum carboxyterminal propeptide of type I procollagen, PICP), bone resorption (serum pyridinoline cross-linked carboxyterminal telopeptide of type I collagen, ICTP), and nonosseous connective tissue synthesis (serum aminoterminal propeptide of type III procollagen, PIIINP) were studied in 82 female twin pairs: 42 monozygotic (MZ) and 40 dizygotic (DZ) twin pairs (mean age, MZ; 48.4 yr; DZ; 45.6 yr). The intraclass correlation coefficients of MZ twin pairs, rMZ, for serum PICP (0.78) and serum ICTP (0.68)

were significantly greater than the corresponding rDZ (0.31 and 0.36, respectively), but a genetic effect on serum PIIINP was not demonstrable. Within DZ twin pair differences in serum PICP predicted differences in lumbar spine bone density ($r = -0.37$); higher serum PICP levels indicating the twin with the lower lumbar spine bone density. Also within pair differences in serum ICTP and PICP predicted differences in bone density at the lumbar spine independent of serum osteocalcin. These data indicate that both synthesis and degradation of type I collagen are genetically determined and that this phenomenon is related to the genetic regulation of bone density. (*J Clin Endocrinol Metab* 78: 1461-1466, 1994)

TWIN (1-6) and family (7-9) studies suggest strong genetic effects on bone mineral density. Moreover we have previously shown that serum osteocalcin, a marker of bone formation, is under strong genetic influence and this is related to the genetic effect on bone mineral density (5). In the twin study of bone turnover indices, we were unable to demonstrate a genetic effect on the bone resorption markers urinary hydroxyproline and calcium excretion. However, these urinary bone resorption markers are relatively nonspecific.

Further evidence for genetic effects on bone turnover stems from our observations of the relationship between osteocalcin levels and variation in the vitamin D receptor gene. We have observed common polymorphisms in the vitamin D receptor gene in a normal population that predict osteocalcin levels (10). In this study higher osteocalcin levels were observed in individuals with a particular vitamin D receptor gene allele, adding further evidence to the genetic regulation of bone turnover.

The organic matrix of bone consists of type I collagen (more than 90%), with the noncollagenous proteins compris-

ing the remaining 10% (11). Recently assays have been developed to detect circulating products of both type I collagen synthesis and degradation. Carboxyterminal propeptide of type I procollagen (PICP) is a globular trimer cleaved extracellularly from the carboxyterminus of procollagen. PICP is not incorporated in bone matrix and circulating levels correlate with bone collagen synthesis rate and osteoblast activity (12-18). The pyridinoline cross-linked carboxyterminal telopeptide of type I collagen, ICTP, is cleaved during degradation of type I collagen and correlates with bone resorption assessed by either histomorphometry or calcium kinetic studies (19, 20). Type III collagen, by contrast, is abundant in vascular and intestinal smooth muscle, skin, uterine tissue, walls of blood vessels and is found in bone only in the marrow cavity (21, 22). Changes in the blood levels of the aminoterminal propeptide of type III procollagen (PIIINP) correlate with those change in type III collagen synthesis (13, 23, 24).

To assess whether genetic effects on bone turnover are detectable with markers of bone collagen turnover we analyzed the correlations between serum PICP and ICTP in identical and nonidentical female twin pairs. Genetic effects on serum PIIINP were also analyzed to assess whether any genetic effect on serum PICP and ICTP was a reflection of nonspecific genetic effects on collagen synthesis and degradation or specific for bone collagen metabolism. Furthermore possible relationships between bone turnover and bone density were analyzed in the same individuals.

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Materials and Methods

One hundred and sixty four female twins [comprising 42 monozygotic (MZ) and 40 dizygotic (DZ) pairs] were studied. The ages of the two groups of twins were similar; MZ: 48.4 ± 13.7 yr; DZ: 45.6 ± 10.3 yr, mean \pm sd). The twins were recruited from the Australian National Health and Medical Research Council Twin Registry and requests through the local media. The data on bone mineral density and genetic effects on osteocalcin and urinary hydroxyproline and calcium excretion on a subgroup of this cohort have been previously published (5). Subjects with a previous history of bone and connective tissue disease, illness or drug use, which could affect bone turnover were excluded from the study. Fifteen MZ twin pairs and 12 DZ twin pairs were postmenopausal. Menopausal status was confirmed by the presence of elevated FSH and LH and low estradiol levels with an absence of menses for at least 12 months. Those subjects with regular menses were considered premenopausal. None of the twin pairs were discordant for menopausal status. Among the postmenopausal twins, there was no significant difference in age (mean \pm sd: MZ 62.0 ± 9.6 yr, DZ 58.2 ± 5.3 yr) or years postmenopause (mean: MZ 12.1 yr, range 1–26 yr, DZ 11.6 yr, range 2–35 yr). None of the postmenopausal subjects was taking sex hormone replacement therapy and no twin pair was discordant, within 24 months, of years since menopause.

Blood samples were collected in the early morning after an overnight fast (25), and stored at -20 C. All twin pair samples were measured in duplicate in the same assay. Serum concentrations of PICP were measured using an equilibrium RIA (26). The sensitivity of the method, defined as the lowest detectable concentration is 1.2 μ g/L. The intra- and interassay coefficients of variation (CV) were 2.7% and 5.2%, respectively. Serum concentrations of ICTP were measured with a recently developed equilibrium RIA (19). This assay uses polyclonal antibodies developed in rabbits against the pyridinoline cross-linked carboxyterminal telopeptide region of type I collagen with the peptide labeled with the chloramine-T method. In a radioimmuno-inhibition assay, serum samples give inhibition curves parallel with the standard antigen, indicating that during normal bone turnover a similar fragment is set free and remains immunochemically intact (19). The intra- and interassay coefficient variation (CV) were 4.8% and 7.7%, respectively. Serum levels of PIIINP were measured with a RIA, selectively detecting the intact PIIINP and high molecular weight antigen forms of PIIINP (27). Intra- and interassay CV were 4.2% and 6.6%, respectively. The separation reagents for ICTP, PICP, and PIIINP were kindly supplied by Orion Diagnostica (SF-90460 Oulunsalo, Finland). Serum osteocalcin was measured as previously described (5).

Bone mineral density at the lumbar spine (L2–L4) and femoral neck was determined by dual-photon absorptiometry (Lunar Radiation, Madison, WI) as previously reported (28).

Of the DZ twin pairs 35 had osteocalcin data, 40 PICP, and 40 ICTP data. Of the MZ twin pairs 36 had osteocalcin data, 42 PICP, and 42 ICTP data. Thirty eight DZ pairs had bone density as well as osteocalcin, PICP, and ICTP data.

Statistical methods

The conventional twin statistical model involves the modeling of an observed quantitative variable trait (Y) as an additive function of genetic effect (G), environmental effect (C), and effect of specific factors related to a particular individual within the twin pair (not shared by members of a twin pair), including measurement error (E). Assuming that G , C , and E are independently normally distributed with zero mean and nonnegative variances $\sigma^2(g)$, $\sigma^2(c)$, and $\sigma^2(e)$, respectively, then the total variance of a variable trait for a zygosity is an additive function of $\sigma^2(g)$, $\sigma^2(c)$, and $\sigma^2(e)$. However, it can be shown that the within pair variance for MZ group is determined by $\sigma^2(c)$ and $\sigma^2(e)$ of that group; whereas the within pair variance for DZ group is determined by partial $\sigma^2(g)$, $\sigma^2(c)$, and $\sigma^2(e)$, where partial $\sigma^2(g)$ includes half of the variance due to additive effect [$\sigma^2(a)$] and three quarter of the variance due to dominance effect [$\sigma^2(d)$]. The relationship in a variable trait between twin 1 (Y_1) and twin 2 (Y_2) as measured by the covariance $\text{Cov}(Y_1, Y_2)$ can be expressed as $\text{Cov}(Y_1, Y_2) = \text{Cov}(G_1, G_2) + \text{Cov}(C_1, C_2)$. Other assumptions in the method are: 1) the additive (no gene interaction) genetic variance within DZ twin pairs is half to that of MZ twins; 2) the environmental covari-

ance of MZ twins is the same as the environmental covariance of DZ twins; and 3) individuals not in the same pair are independent with respect to genetic and environmental effects. These assumptions can be translated into statistical terms as: the correlation of G_1 and G_2 for MZ pairs is 1 whereas the correlation of G_1 and G_2 for DZ pairs is 0.5; also the correlation of C_1 and C_2 is 1, independent of zygosity; that is $\text{Cov}(C_1, C_2)_{mz} = \text{Cov}(C_1, C_2)_{dz}$. Hence $\text{Cov}(MZ) = \sigma^2(g) + \sigma^2(c)$ and $\text{Cov}(DZ) = 0.5 \cdot \sigma^2(g) + \sigma^2(c)$. Thus, $\text{Cov}(MZ) = \text{Cov}(DZ)$ if and only if $\sigma^2(g) = 0$. In other words, a significant difference in covariances (and therefore, correlations) between MZ and DZ twin pairs is consistent with a significant genetic influence on population variation in a trait, providing that total variance is not related to zygosity, and that environmental influences are equal in both MZ and DZ twin pairs.

Estimation and hypothesis testing

All variable traits (PICP, ICTP, and PIIINP) were found to be non-normally distributed, therefore a logarithmic (base 10) transformation was applied to the data. Total variances of a variable trait for MZ and DZ twins were firstly partitioned into two components: between pairs (BMZ and BDZ) and within pairs (WMZ and WDZ). The intraclass correlation coefficient for each zygosity was then derived as $r_{MZ} = (\text{BMZ} - \text{WMZ})/(\text{BMZ} + \text{WMZ})$ and $r_{DZ} = (\text{BDZ} - \text{WDZ})/(\text{BDZ} + \text{WDZ})$. The index of heritability was then estimated by the Falconer's formula $H^2 = 2(r_{MZ} - r_{DZ})$ (29). Test of equality of phenotypic variances $F = (\text{WDZ} + \text{BDZ})/(\text{WMZ} + \text{BMZ})$ was calculated with numerator and denominator degrees of freedom according to Haseman and Elston (30). It was observed that the variance for each variable trait was independent of zygosity. Testing for the effects of genetic factor [$\sigma^2(g) = 0$] was done via the statistic $F = \text{WDZ}/\text{WMZ}$ with numerator and denominator degrees of freedom as the number of twin pairs in each zygosity (n_{DZ} and n_{MZ}), respectively.

In addition to the traditional analysis of variance, we also analyzed the data by model fitting approach. In this analysis, we fitted three parsimonious models as follows:

$$\text{Model 1: } Y = m + G + C + E$$

$$\text{Model 2: } Y = m + C + E$$

$$\text{Model 3: } Y = m + G + E$$

where m is the overall mean; G , C , and E are as described earlier. The parameters G , C , and E were estimated by the least squares methods proposed by LaBuda *et al.* (31) and Cherney *et al.* (32).

By the normal statistical theory, test for significance of G [$\sigma^2(g) = 0$] can be done by comparing the residual mean squares of model 1 and model 2 via the F statistic (33). All computations were done via the SAS statistical analysis system (34).

Results

There was no significant relationship between age and either serum PICP, ICTP, and PIIINP. Serum PICP, ICTP, and PIIINP were not significantly different between pre- and postmenopausal women overall (Table 1). However, within the first 10 yr of the menopause serum PICP and ICTP levels tended to be higher than in premenopausal women and to decline in those women more than 10 yr postmenopause (Table 1). Serum osteocalcin, PICP, and ICTP data were available on 37 MZ and 33 DZ twin pairs. There was a significant correlation between serum osteocalcin and PICP ($r = 0.29$, $P = 0.004$), which remained when only one twin of each MZ twin pairs was included in the analysis. There was however no relationship between serum osteocalcin and ICTP ($r = 0.16$, $P = 0.09$).

The within twin pair analysis for serum PICP revealed that the MZ intraclass correlation coefficient, r_{MZ} (0.78), was

TABLE 1. Serum PICP, ICTP and PIIINP in premenopausal and postmenopausal women who were less than (≤ 10 YPM) and more than (>10 YPM) 10 yr since menopause

	Premenopausal (n = 83)	Postmenopausal	
		≤ 10 YPM (n = 20)	>10 YPM (n = 19)
PICP	126.0 \pm 4.8	142.5 \pm 9.9	125.2 \pm 7.6
ICTP	2.84 \pm 0.12	3.02 \pm 0.26	2.37 \pm 0.23
PIIINP	3.52 \pm 0.10	3.2 \pm 0.11	3.60 \pm 0.27

All values are expressed in micrograms per (mean \pm SEM), with the number of subjects in parentheses. There were no statistically significant differences between any groups.

significantly greater ($P = 0.008$) than rDZ (0.31). For serum ICTP, rMZ (0.68) was significantly greater ($P = 0.01$) than rDZ (0.36) (Fig. 1 and Table 2). The Falconer's index of heritability indicated that genetic factors were responsible for the majority of the variance in the observed data for both serum PICP and ICTP (Table 2); genetic factors contributing 95% of the variance in serum PICP and 64% of the variance in serum ICTP levels. Genetic factors contributed only 35% of the total variance in serum PIIINP levels. Also model fitting analysis indicated that models incorporating a genetic source of variance best described the observed data for both PICP and ICTP but not PIIINP (Table 3). The model incorporating genetic, common environmental and other specific factors best fitted the observed PICP and ICTP data. Also, removal of the genetic source of variance reduced the "goodness of fit" of the model. This confirms that genetic factors contribute significantly to the observed variance in these markers of type I collagen turnover.

When the data on the postmenopausal women were analyzed alone, rMZ for serum PICP and ICTP (0.67, 0.75, respectively) remained significantly ($P < 0.05$) greater than rDZ (0.28, 0.48, respectively). For serum PIIINP, rMZ (0.35) was no greater than rDZ (0.27) in the postmenopausal women.

A significant correlation was observed between serum PICP and ICTP ($r = 0.22$, $P = 0.015$). To analyze whether the genetic effect on both serum PICP and ICTP was the result of a single gene or set of genes cross-twin analysis was performed. Serum PICP in one twin was compared to serum

ICTP in her cotwin for both MZ ($n = 84$) and DZ ($n = 80$) twins. The rMZ (0.47, $P = 0.0001$) was significantly greater ($P = 0.001$) than rDZ (0.04, $P = 0.68$), consistent with common genetic influences on both serum PICP and ICTP levels.

The possible relationship between genetic effects on serum PICP and ICTP and bone density was then examined. Given the predominant genetic effect on ICTP, PICP, and bone density, the within DZ pair difference should reflect genetic variance. To avoid bias in twin selection, the data were inputted twice in a cross-over fashion, in the first input an individual within a pair was assigned as twin 1 or twin 2; in the second input the respective individual was assigned as twin 2 and twin 1. Therefore, within DZ twin pair differences in both markers were compared to the within DZ twin pair differences in both femoral neck and lumbar spine bone mineral density. The twin with the higher serum PICP level had a lower bone mineral density at lumbar spine (Fig. 2), and a similar trend was seen at the femoral neck ($r = -0.32$, $P = 0.08$). There was a similar but nonsignificant trend for higher serum ICTP levels in those twins with the lower bone density at both the lumbar spine ($r = -0.29$, $P = 0.12$) and femoral neck ($r = -0.27$, $P = 0.15$). The relationship between serum PICP, ICTP, and bone density differences in DZ twins was examined further to assess whether this relationship was independent of serum osteocalcin differences. Using stepwise regression technique, we found that the difference in lumbar spine (Δ LS) BMD was negatively and independently correlated with the differences (Δ) in serum osteocalcin, ICTP and PICP: Δ LS BMD = 0.03 - 0.001 Δ PICP - 0.03 Δ ICTP - 0.01 Δ osteocalcin; $R^2 = 0.55$; $P = 0.01$; 0.02; 0.0001 for Δ PICP, Δ ICTP, Δ osteocalcin, respectively. The difference in femoral neck density (Δ FN BMD) was negatively correlated with within pair difference in serum osteocalcin only; Δ FN BMD = 0.01 - 0.01 Δ osteocalcin; $R^2 = 0.39$; $P = 0.0001$ for Δ osteocalcin. (Notice that the estimated SE for the regression parameters and hence their P values have been adjusted by the product of SE and df of double-entered/df single-entered^{1/2}).

In order to check the consistency of the obtained equations, we also analyzed by the random assignment method. In this

FIG. 1. Indices of type I and type III collagen synthesis and degradation in twins. Within MZ and DZ twin pair correlations about the line of identity for serum PICP, ICTP, and PIIINP are shown. The line of identity is shown in each graph and the values are micrograms per L (log transformed).

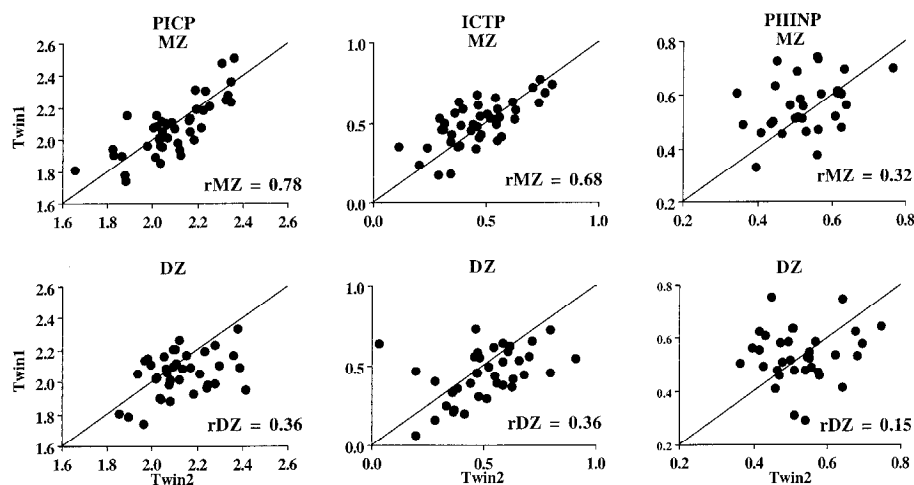


TABLE 2. Results of partition of variance and estimated heritability

Zygoty	Statistic	PICP	ICTP	PIIINP
MZ	Number of pairs	42	42	31
	Mean \pm SD	2.08 ± 0.17	0.48 ± 0.15	0.54 ± 0.15
	Between MS	0.051	0.038	0.013
	Within MS	0.006	0.007	0.007
	rMZ	0.78	0.68	0.32
DZ	Number of pairs	40	40	33
	Mean \pm SD	2.09 ± 0.14	0.46 ± 0.18	0.52 ± 0.10
	Between MS	0.025	0.043	0.011
	Within MS	0.013	0.021	0.008
	rMZ	0.31	0.36	0.15
Estimated heritability		0.95	0.64	0.35
<i>P</i> value of genetic effect ^a		0.008	0.01	0.30

Data presented were based on logarithmic (base 10) transformation. SD, Standard deviation; MS, mean square obtained from the analysis of variance.

^a *P* values derived from testing the hypothesis that $\sigma^2 = 0$ or index of heritability $H^2 = 0$.

TABLE 3. Results of model fittings

Variable	Residual mean square ($\times 10^6$)			Comparison of models (<i>P</i> value) ^a	
	Model 1: G + C + E	Model 2: C + E	Model 3: G + E	Model 1 vs. model 2	Model 1 vs. model 3
PICP	141.2	153.4	141.0	0.0002	0.38
ICTP	20.1	20.7	20.0	0.02	0.92
PIIINP	91.4	91.8	90.8	0.21	0.63

Model 1, $Y = \text{overall mean} + \text{genetic factor (G)} + \text{common environment (C)} + \text{error (E)}$. Model 2, $Y = \text{overall mean} + \text{common environment (C)} + \text{error (E)}$. Model 3, $Y = \text{overall mean} + \text{genetic factor (G)} + \text{error (E)}$.

^a Comparison of model 1 vs. model 2 is a test for genetic effect, whereas comparison between model 1 vs. model 3 is a test for common environmental effect.

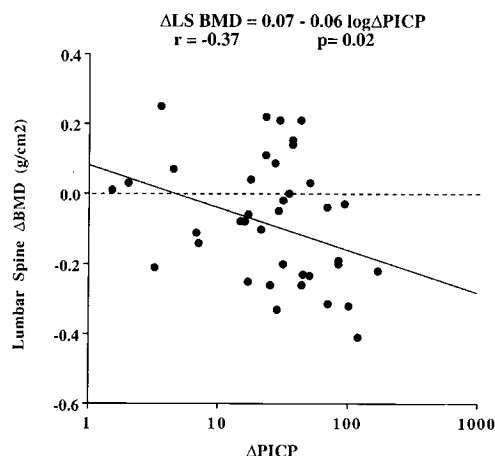


FIG. 2. The relationship between intrapair differences in DZ twins in serum PICP and intrapair differences in bone mineral density at the lumbar spine. In this representation twins were selected so as to result in a positive difference in serum PICP and the x axis is logarithmic (difference in serum PICP in micrograms per L).

method, an individual within a twin pair was assigned as twin 1 or twin 2 by the uniformly distributed random number

generator. The assignment was repeated for 1000 iterations. In each iteration the above regression equations were fitted and hence its estimated parameters were obtained. In all 1000 iterations, we found that the residual mean square varied by only 1%; indicating the obtained equations are highly consistent.

Discussion

Using the twin model we have previously shown that the majority of the population variance in osteocalcin levels in women is due to genetic factors (5), supporting genetic effects on bone turnover. In further support of a genetic effect on both bone formation and resorption, our current data show that for two indices of bone turnover, serum ICTP and PICP, the correlation between identical twin pairs significantly exceeded that between nonidentical twin pairs.

The assumption of the analysis of within MZ and DZ twin pair correlations for a trait is that a simple genetic model applies and that environmental influences are not more similar within MZ twin pairs. DZ twins share, at most, half their genes, whereas MZ twins are genetically identical. Therefore, when rMZ is significantly greater than rDZ it is assumed genetic factors contribute to the variance in the measured trait. Moreover for a simple genetic model to apply rMZ should be double rDZ. However, when rMZ is more than double rDZ exceptions to the simple genetic model should be considered. These include the assumption of equal common environments of MZ and DZ twins, gene-gene or gene-environment interaction or dominant inheritance. In a subgroup of the twins studied we have found no evidence for an influence of zygosity on variance in environmental factors such as calcium intake, physical activity, and tobacco consumption (35). The observed rMZ for serum PICP tended to be more than twice rDZ, however, we could not demonstrate the significance of this observation statistically ($P = 0.16$). Type I procollagen, from which PICP is derived, contains two kinds of polypeptide chain, two $\alpha 1(I)$ and one $\alpha 2(I)$ chains. As type I collagen is the product of two genes, serum PICP may be influenced by least these two genes. We may have expected therefore observed rMZ for serum PICP to be more than twice rDZ consistent with gene-gene interaction, in this case the interaction between the two genes required for synthesis of type I collagen.

In the present study, the serum ICTP level, a sensitive index of bone resorption (20), was genetically influenced. ICTP is a trimer containing peptides from two collagen molecules and a cross-link with a pyridinoline structure. Measurement of the various pyridinoline cross-links, cleaved from ICTP and similar peptides, has also been used recently as a bone resorption marker (36–38) and levels of ICTP in serum tend to correlate with urinary deoxypyridinoline cross-links measured by HPLC (19). Serum ICTP is cleared in the kidney and elevations may occur in renal insufficiency. However, all subjects in the present study had normal renal function.

Genetic effects on both serum PICP and ICTP could operate at the level of clearance and excretion. This seems unlikely, since ICTP is cleared by the kidney (19), whereas

PICP, as a large glycoprotein, is taken up by the liver endothelial cells via a mannose receptor (39). Moreover, our analysis indicates that a single gene or set of genes contributes to the observed genetic effect in both parameters. Also if the genetic effect was at the level of clearance one would not expect the relationship between serum PICP, ICTP, and bone density observed in DZ twins. When serum PICP in one twin was compared to serum ICTP in her cotwin the within pair correlation in MZ twins was significantly greater than within DZ pairs supporting the idea that the genetic effects on serum PICP and ICTP are due to the same gene or set of genes. Our data therefore suggest that a common genetic influence underlies the regulation of type I collagen synthesis and degradation, presumably at the level of the regulation of bone turnover. That ICTP and PICP independently predict spinal bone density reflects their correlation with different aspects of bone remodeling and does not counter the hypothesis of common genetic regulation of serum PICP and ICTP. Finally if the genetic effect observed related to generalized effects on collagen synthesis we would have expected rMZ to be significantly greater than rDZ for circulating PIIINP. This was not the case however.

Previously we noted that within DZ twin pair differences in serum osteocalcin, presumably reflecting genetic variance, predicted differences in bone mineral density (5). In the present study within DZ twin pair differences in serum PICP predicted differences in lumbar spine bone density; the twin with the higher index had the lower bone density. Also, we found that within pair differences in both serum PICP and ICTP predicted differences in bone density at the lumbar spine in DZ twins independent of differences in serum osteocalcin. Serum osteocalcin remained a significant predictor at the femoral neck. Caution should be exercised in the extrapolation of the proportion of the variance in bone density at each site attributable to differences in bone turnover markers as these values relate to the twin population under study and may not be directly transferable to other populations. However, if the common genetic factors were mediating the genetic influences on serum osteocalcin, PICP, and ICTP, independent relationships with bone density differences in bone density in DZ twins would not be expected. These data therefore suggest that the genetic effect reflected in serum PICP and ICTP levels, and its effect on bone density, at least at the lumbar spine, may be independent of the genetic effect on serum osteocalcin. In this regard we have found a relationship between vitamin D receptor polymorphisms and serum osteocalcin levels in normal subjects (10). However, preliminary analysis suggests that no similar relationship exists between the same polymorphisms and serum PICP or ICTP levels in a smaller group of subjects. This implicates other genetic influences.

It has been argued that the genetic effect on bone mass may stem from minor structural mutations at the bone matrix level, that is qualitative differences (mutations) in collagen structure, analogous to osteogenesis imperfecta subtypes. This concept relates to recent case reports of mild osteogenesis imperfecta variants presenting as severe postmenopausal osteoporosis (40, 41). However, data to suggest that variation

in the structural properties of bone collagen underlies the genetic variation of bone density in normal adults are lacking. The current data and our previous observations (5) on bone turnover indices and their relationship to bone density in twins, suggest that regulation of bone turnover and the regulation of collagen synthesis and degradation, rather than collagen structure *per se*, are the major site of the genetic influence. Moreover we have also recently reported that the genetic effect on osteocalcin levels in normal subjects is related to allelic variation in the vitamin D receptor gene (10) and that this effect also relates to the genetic effect on bone density in twins. Therefore, in normal subjects, the evidence to date supports a major role for genetic factors in the regulation of bone remodeling.

In this study the population variance in specific markers of type I collagen synthesis and degradation in women, serum PICP and ICTP, respectively, was found to be due to genetic factors. Moreover this could be assigned to a common gene or set of genes and relates to the genetic effect on bone density. Given the relationship with serum osteocalcin levels, further analysis with regard to vitamin D receptor polymorphism should provide valuable insight. These data support the hypothesis that the genetic effect on bone mass relates to the regulation of bone turnover and indicate that attention should be directed toward regulation of bone remodeling to further understand the molecular basis of the population variance in bone density.

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