Bone Turnover in Postmenopausal Osteoporosis

Effect of Calcitonin Treatment

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Abstract

To investigate the effectiveness of calcitonin treatment of postmenopausal osteoporosis in relation to bone turnover, we examined 53 postmenopausal osteoporotic women before and after one year of therapy with salmon calcitonin (sCT), at the dose of 50 IU every other day. Baseline evaluation revealed that 17 (32%) patients had high turnover (HTOP), and 36 (68%) normal turnover osteoporosis (NTOP) as assessed by measurement of whole body retention (WBR) of ^{99m}Tc-methylene diphosphonate. The two groups did not differ in terms of bone mineral content (BMC) measured by dual photon absorptiometry at both lumbar spine and femoral diaphysis. However, HTOP patients had higher levels of serum osteocalcin (OC) and urinary hydroxyproline excretion (HOP/Cr). Multivariate regression analysis showed no correlation between parameters of bone turnover (WBR, OC, HOP/Cr) and both femoral and vertebral bone density; the latter being negatively correlated only with the years elapsed since menopause (R^2 = 0.406). Treatment with sCT resulted in a significant increase of vertebral BMC in the 53 patients taken as a whole group (±7%, $P < 0.001$). When the results obtained in HTOP and NTOP were analyzed separately, only those with HTOP showed a marked increment of spinal BMC (+22%, $P < 0.001$), NTOP subjects neither gained nor lost bone mineral during the study. Femoral BMC decreased in the whole group after sCT therapy (−3%, $P < 0.003$). However, HTOP patients maintained initial BMC values, whereas those with NTOP lost a significant amount of bone during the study period (−5%, $P < 0.001$). The increase of vertebral bone mass was associated with a marked depression of bone turnover detectable in both subsets of patients and in the whole group. In conclusion: (*a*) assessment of bone turnover cannot help predict the severity of bone loss in postmenopausal osteoporosis; (*b*) calcitonin therapy appears to be particularly indicated for patients with high-turnover osteoporosis, resulting in a net gain of bone mineral in the axial skeleton and a slowing of bone loss in the appendicular bones.

Introduction

Postmenopausal osteoporosis is characterized by a reduction in bone mass following natural or artificial menopause. Histomorphometric studies designed to define bone remodeling (bone turnover) in untreated osteoporosis demonstrated the heterogeneous nature of this disorder, which ranges from reduced to accelerated bone remodeling rates (1–3). It is becoming increasingly obvious that the available spectrum of pharmacologic treatments are not completely effective in reversing the accelerated bone loss that characterizes postmenopausal or involutional osteoporosis. A more rational approach to effective therapy might be to use specific drug regimens for specific states of bone turnover.

Calcitonin has been reported to be effective in the treatment of postmenopausal osteoporosis in both short-term, noncontrolled (4–6) and long-term, placebo-controlled studies (7–9). However, Jowsey et al. (10) failed to obtain any beneficial effects with this drug when compared with calcium supplementation alone in 26 women with osteoporosis, and Wallach et al. (11) obtained an increase in total body calcium in only half of treated patients. These variable results probably can be attributed not only to criteria used for selection of the study population, but also to the heterogeneous nature of the osteoporotic skeletal lesions.

Calcitonin affects bone metabolism by depressing bone resorption (12–14). In fact, the efficacy of calcitonin therapy has been established primarily in conditions characterized by high turnover rates, such as Paget's disease of bone (15–17) and hypercalcemia of various etiology (18–20). Since postmenopausal osteoporosis is a heterogeneous disorder in terms of bone remodeling, we wondered whether subjects with osteoporosis and higher rates of bone turnover would respond more favorably to calcitonin treatment than those with low turnover rates.

Bone turnover is usually assessed by histomorphometric analysis of bone biopsies, which is probably the most reliable method available at present. However, bone biopsy is an invasive procedure, and it yields information only on a restricted area of bone, which may not be representative of the entire skeleton. Combined kinetic and calcium balance studies have been used to assess bone remodeling rates (4, 21), but these methodologies are unsuitable in a routine clinical setting.

In the last decade, skeletal uptake of bone-seeking radiopharmaceuticals, expressed as whole body retention (WBR)[1] of the tracer, has been proposed as a noninvasive and effective method for measurement of bone turnover (22–26). More recently, a Danish group (27, 28), on the basis of an early report of Caniggia and Vattimo (29), demonstrated that the simple determination of 24-h urinary excretion of ^{99m}technetium–

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1. *Abbreviations used in this paper:* BMC, bone mineral content; BMC-FD, bone mineral content of the femoral diaphysis; BMC-LS, bone mineral content of the lumbar spine; HOP/Cr, hydroxyproline/creatinine ratio; HTOP, high-turnover osteoporosis; MDP, methylene diphosphonate; NTOP, normal turnover osteoporosis; OC, osteocalcin; sCT, salmon calcitonin; WBR, whole body retention; YSM, years since menopause.

methylene diphosphonate (^{99m}Tc-MDP) is highly correlated to WBR, estimated by whole-body counting. This allows a great simplification of the method.

In the present investigation we used this method to study the effects of one-year treatment with salmon calcitonin (sCT) on bone turnover in a series of 53 postmenopausal women with osteoporosis. The aims of this investigation were twofold: first, to determine whether the rate of bone remodeling could be correlated with bone mineral content (BMC), as assessed by dual photon absorptiometry of the lumbar spine and femoral shaft, and thus whether WBR can be used to predict the severity of postmenopausal bone loss; and second, to determine whether long-term sCT treatment could be more effective in osteoporotic patients with higher turnover rates (HTOP), compared with those with normal or low bone-remodelling rates (NTOP), thus providing a more selective indication for this drug in the postmenopausal osteoporotic population.

Methods

Patients. From a large number of patients referred to the Center for the Diagnosis and Treatment of Osteoporosis at the University of Siena, Italy, a cohort of 79 consecutive postmenopausal women (aged 46–66 yr) with radiologically evident osteoporosis (presence of vertebral wedging or crush fractures) were selected to participate in this study. Menopausal state was determined by clinical history, and defined as absence of menses for at least one year before entering the study. Criteria of exclusion were: previous treatment with hormones, and use of calcitonin or other drugs active on bone metabolism for at least two years before the beginning of the study. Besides the presence of osteopenia, the patients were in general good health. All gave their informed consent before entering the study. After the baseline evaluation all of them were started on synthetic sCT (Calcitonina Sandoz; Sandoz Prodotti Farmaceutici, Milan, Italy) 50 IU s.c. every other day for 12 mo. The dietary intake of calcium was maintained within 500 and 1,000 mg/d throughout the entire period of study. At 6 and 12 mo the patients returned to the Center for measurement of BMC. WBR and parameters of bone turnover were reevaluated only at one year. Fifty-three patients finished the study. Of these, three refused a second injection of the radioactive tracer. The baseline characteristics of the 26 drop-outs were not statistically different from those of the study population, and the effect of including data from drop-outs in the analysis was insignificant.

Controls. As control population we studied 24 normal perimenopausal (6 premenopausal, 18 postmenopausal) women, aged 40–60 years, with no evidence of osteoporosis or other bone disease by x-ray of the entire skeleton and dual photon densitometry of vertebral bodies. Their clinical and biochemical features are illustrated in Table I. Informed consent was obtained from all subjects for determination of WBR and for the biochemical studies.

Bone mineral content. BMC of the lumbar spine (BMC-LS) and femoral diaphysis (BMC-FD) was measured by dual photon absorptiometry, using the BMC-LAB 22a system (Novo Diagnostic, Bagsvaerd, Denmark), which uses ^{153}Gd as radioactive source. Bone mineral density was calculated from scans of vertebrae L2, L3, and L4 (lumbar spine), and femoral mid-shaft (femoral diaphysis). Fractured vertebrae were excluded from the measurements. The precision of the method is 3.18% for the lumbar spine and 1.88% for the femoral shaft, as detailed elsewhere (30).

Whole-body retention. WBR of ^{99m}Tc-MDP was assessed according to the method of Hyldstrup et al. (27), with modifications, as follows. After voiding, patients were injected with an intravenous dose of 0.5–1.0 mCi ^{99m}Tc-MDP (MedroTek; Sorin Biomedica, Saluggia, Italy), and 24-h urine collection was started immediately. Particular care was given to the first 3–4 h of urine collection, since > 50% of the injected dose is excreted during that period of time (29). At the end of the collection period, the activity of 2-ml urine sample was counted in a well-type, gamma scintillation counter (Tri-Carb; Packard Instruments, Downers Grove, IL). A sample taken from the injected solution was counted as standard together with the urine sample. The total injected dose and urinary excretion of ^{99m}Tc-MDP were extrapolated, and WBR was calculated as 100 × (1 − total urine counts/total injected counts); which represents the fraction, in percent, of the injected dose retained in the body 24 h after injection. The precision of the method was calculated by duplicate measurements in normals (men and premenopausal women) within a period of 3–6 wk. The coefficient of variation was 2.77±0.54% (n = 19) for the overall population, and 2.99±0.99% (n = 8), and 2.61±0.64% (n = 11) for subjects with low and high retention values, respectively.

Table I. Parameters of Bone Metabolism in Normal Perimenopausal and Postmenopausal Osteoporotic Women

Parameter	Normals (n = 24)	Osteoporotics (n = 53)	Unpaired t test	One-way ANOVA with age covariate*
Age (*yr*)	52.9±6.4	56.7±5.4	t = 2.65 P = 0.010	—
BMC-LS (*g/cm²*)	0.90±0.06	0.58±0.13	t = 11.348 P < 0.001	F = 121.27 P < 0.001
BMC-FD (*g/cm²*)	1.43±0.08	1.06±0.15	t = 11.068 P < 0.001	F = 105.15 P < 0.001
WBR (*% injected dose*)	27.5±4.8	33.3±7.4	t = 3.54 P < 0.001	F = 9.267 P = 0.003
OC (*ng/ml*)	5.4±1.8	7.7±4.6	t = 2.295 P = 0.025	F = 3.852 P = 0.053
HOP/Cr (*mg/g*)	14.3±4.8	19.8±8.8	t = 2.880 P = 0.005	F = 6.451 P = 0.013

Data are mean±SD.
* The effect of age was significant only on WBR variability (P = 0.031).

Biochemical analyses. Blood and urine samples were collected at 8 a.m., after an overnight fast. All samples were stored at −20°C until the day of the assay. Serum osteocalcin (OC) was measured by a radioimmunoassay using the Osteocalcin RIA kit (Immuno Nuclear Corp., Stillwater, MN). Urinary hydroxyproline was determined in 24-h urine samples according to the method of Prockop and Udenfriend (31), using the Hypronosticon kit (Organon, Baxtel, The Netherlands), and expressed as hydroxyproline/creatinine ratio (HOP/Cr; mg/g). Creatinine was assayed using the Creatinine-kine test (Sclavo, Siena, Italy). All these procedures have been previously described in more detail (30).

Statistical analysis. Group means were compared using Student's t test for dependent or independent samples. Analysis of covariance was used to compare the normal versus the osteoporotic population (controlling the effect of age as covariate), and Scheffé's multiple range test was used to analyze the effect of age on WBR. The interrelations of bone mass with markers of bone turnover were analyzed by applying linear regression models (simple and Pearson partial correlation coefficients), and the contribution of each factor to bone mass variability was determined using a stepwise selection analysis. Data were managed and analyzed using a statistical analysis software (Statgraphics, version 2.1 1986; STSC Inc., Rockville, MD).

Results

Patients with postmenopausal osteoporosis as a group had lower mineral content in both axial and appendicular bones, and higher levels of WBR, serum OC and urinary hydroxyproline compared with the normal subjects by unpaired t test (Table I). Since the osteoporotic patients were significantly

older than the normal subjects, an analysis of covariance was performed on the same data, keeping the age as covariate. Even in this case a significant difference was found between the two groups for spinal and femoral BMC, WBR, and hydroxyproline, whereas the P value for OC was slightly above the 0.05 limit.

The potential effect of patients' age on WBR was analyzed in both control and osteoporotic populations. The distribution of data was not age-related (r = 0.045 for normals; 0.178 for osteoporotics). Also, analysis of variance on WBR data stratified for age in five 5-yr groups showed no significant grouping effect (controls: F = 0.381, P = 0.768; osteoporotics: F = 1.172, P = 0.330), and multiple range analysis indicated homogeneity in the two populations. Thus, the contribution of age to WBR was considered not significant in the age range of the study population.

To investigate whether bone turnover was an important determinant of mineral loss in our osteoporotic patients, we studied the interrelations of both axial and appendicular bone mass with the parameters of bone turnover and with the years since the menopause (YSM). Both simple and partial correlation coefficients were calculated, using simple and multiple regression analysis. In the simple regression format (Table II), a strong negative correlation was found between bone mineral content of the spine and YSM. Also, vertebral BMC was weakly albeit significantly correlated with both femoral BMC and WBR. The correlation with YSM was not altered in the partial correlation model, controlling for markers of bone turnover (Table III). On the contrary, when the effects of age and YSM were weighed, the correlation between spinal BMC and WBR was lost, suggesting that the weak interrelationship found in the simple regression analysis was probably accounted for by an effect of age and/or YSM on WBR. No correlation was found for vertebral BMC vs. either OC or HOP/Cr, and more interestingly, between femoral BMC and YSM, in both the simple and the partial regression analysis (Tables I and II).

WBR was strongly related to both OC and HOP/Cr, thus confirming its validity as marker of bone remodeling. Also, WBR, but neither OC nor HOP/Cr, showed a significant correlation with YSM.

Table II. Correlation Coefficients of Clinical and Biochemical Estimates of Bone Metabolism in 53 Postmenopausal Osteoporotic Women

Parameter	BMC-FD	YSM	OC	HOP/Cr	WBR
BMC-LS	0.313	−0.637	0.155	−0.091	−0.287
	(0.023)	(<0.001)	(NS)	(NS)	(0.037)
BMC-FD	—	−0.267	−0.077	−0.011	−0.260
		(0.053)	(NS)	(NS)	(0.060)
YSM	—	—	0.138	0.042	0.327
			(NS)	(NS)	(0.017)
OC	—	—	—	0.582	0.597
				(<0.001)	(<0.001)
HOP/Cr	—	—	—	—	0.653
					(<0.001)

Significance levels shown in parentheses.

Table III. Pearson Partial Correlation Coefficients Between Bone Mineral Density and Parameters of Bone Turnover in Postmenopausal Osteoporosis

Parameter	BMC-LS	BMC-FD
YSM*	−0.59‡	−0.16
WBR§	−0.15	−0.21
OC§	−0.09	−0.05
HOP/Cr§	−0.08	−0.01

* Controlling for WBR, OC, and HOP/Cr.
‡ $P < 0.001$.
§ Controlling for age and YSM.

The proportional independent contribution of each variable to BMC was determined by applying stepwise variable selection analysis (Table IV). According to their high independent correlation with spinal BMC, years since menopause alone furnished about 40% of the variability of vertebral BMC, giving a multiple regression coefficient of 0.406. When age was added to the model, only a further 3% increase of correlation was achieved, and the estimated coefficient was not significant. The same result was obtained forcing WBR, OC, and HOP/Cr into the model, their overall contribution being < 1% of the total BMC-LS variability. Thus, the final model included only YSM as independent variable. It appears then, that the most important contributor to vertebral bone loss is the time elapsed since menopause, rather than bone turnover.

The osteoporotic patients were then divided into two groups, according to their WBR values. The cut-off value was established at 37.22%, which corresponds to the upper limit of the 95% confidence interval in the normal population. As shown in Fig. 1, 17 patients (32%) had WBR above the upper 95% confidence limit, and thus were considered as having high-turnover osteoporosis (HTOP); the other 36 patients (68%) were grouped as normal-turnover osteoporotics (NTOP).

The two groups of osteoporotic patients were compared for axial and appendicular bone mass, age, and years since menopause, as assessed at the initial visit (Table V). None of the above were statistically different in the two groups. Patients with HTOP, however, had higher serum OC and urinary HOP/Cr, as expected from the high correlation of each of these parameters with WBR.

Table IV. Stepwise Selection of Variables Contributing to Vertebral BMC Variability: Final Model

Included in model				Not included		
Variable	Estimated coefficient	SE	P	Variable	Partial correlation	P
Constant	0.71926	0.0274	<0.001	Age	0.2026	NS
YSM	−0.01773	0.0030	<0.001	WBR	0.1075	NS
				OC	0.0879	NS
				HOP/Cr	0.0841	NS

R^2 = 0.406; SE = 0.011; degrees of freedom = 51.

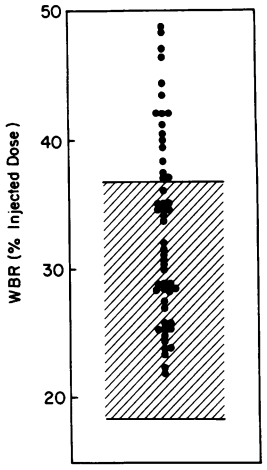

Figure 1. WBR of ^{99m}Tc-MDP in 53 patients with postmenopausal osteoporosis, as compared with the 95% confidence interval (shaded area) of WBR measured in 24 normal perimenopausal women, calculated as mean±2SD.

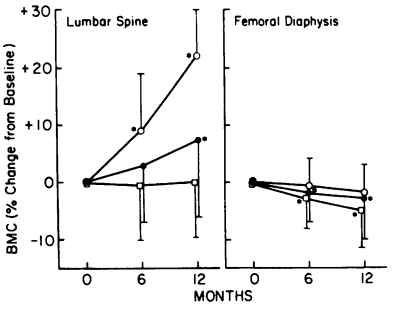

Figure 2. Percent changes in BMC of the lumbar spine (*left*) and femoral diaphysis (*right*), in relation to bone turnover, in a group of postmenopausal osteoporotic women treated with sCT for 1 yr. (○) HTOP (n = 17); (□) NTOP (n = 36); (●) pooled groups (n = 53). Data are mean±SD. *P < 0.01 vs. time 0 (one-sample t-test for mean = 0; t-test for paired data on the actual BMC values gave the same result).

The effect of one year of treatment with sCT on BMC are illustrated in Fig. 2. When data were analyzed considering the 53 patients as a whole group, independently of bone turnover, BMC of vertebral bodies was increased by 2.8±10.3% at 6 mo, and 7.4±14.2% at one year. The increment of bone mass was significant only at 1 yr ($P < 0.001$). On the contrary, a progressive and significant decrease of bone mineral was detected at the femoral diaphysis: −2.2±4.7% at 6 mo and −3.0±6.9% at 12 mo of sCT treatment. However, when the study population was grouped according to bone turnover, a more pronounced increase of spinal BMC was observed in HTOP patients compared with the group as a whole: +9.6±7.5% at 6 mo; +22.4±9.9 at 1 yr; whereas NTOP patients showed no significant changes (−0.4±9.9% at 6 mo; +0.3±9.6% at 12 mo). BMC of appendicular skeleton significantly decreased in the NTOP group (−2.8±4.5% and −5.3±6.4% at 6 and 12 mo, respectively), but it remained constant during the year of treatment in the HTOP group (−0.7±5.0% and +1.9±5.1% at 6 and 12 mo).

Table VI illustrates the changes induced by sCT on markers of bone turnover. Consistent with the observed effects on vertebral bone mass, the major effect of SCT was obtained in the HTOP group, who experienced a marked reduction in WBR, OC, and HOP/Cr after 1 yr of treatment. A significant decrease of bone turnover was also observed in the NTOP patients, and when all the study population was analyzed as whole group. Furthermore, a strong correlation was found between changes of vertebral BMC and changes of WBR, expressed as percent variation from baseline, in the whole population (Fig. 3). Surprisingly, this correlation was significant for the NTOP group ($r = -0.41$, $P = 0.016$), but not for the HTOP patients ($r = 0.33$, $P = 0.208$). This discrepancy might be due to the smaller number of patients, as well as to the narrow range of WBR changes. As evidenced in Fig. 3, all HTOP patients, as well as > 50% of NTOP subjects, showed an increment in bone mass associated with a decrease of turnover. Bone mass decreased in nine NTOP patients, despite a slowing of the bone remodeling rate. In only six patients, WBR increased after 1 yr on sCT. In these cases either no changes or slight decreases (three patients) of BMC were observed.

Table V. Clinical, Functional, and Biochemical Parameters of Patients with HTOP and NTOP

Parameter	NTOP (n = 36)	HTOP (n = 17)
Age (*yr*)	56.4±5.4	57.5±5.6
YSM	7.3±4.3	9.4±5.8
BMC-LS (*g/cm²*)	0.59±0.13	0.54±0.13
BMC-FD (*g/cm²*)	1.01±0.18	1.07±0.15
OC (*ng/ml*)	6.46±3.0	11.6±6.2*
Urinary HOP/Cr (*mg/g*)	16.3±5.5	30.4±8.8*

Data are mean±SD.
* $P < 0.001$; unpaired t test.

Discussion

This study confirms the heterogeneity of bone remodeling in postmenopausal osteoporosis, and demonstrates that the severity of bone loss is not directly related to higher turnover rates in these patients. It also demonstrates that long-term treatment with sCT is effective in producing a gain of bone mass of the axial skeleton in patients with high bone remodeling. In subjects with normal turnover rates, sCT can prevent bone loss in the vertebrae but not in the femur.

Measurement of WBR from the urinary excretion of radiolabeled diphosphonate has been established as a simple and effective method for evaluation of bone remodeling (27–29, 32). Skeletal uptake of diphosphonate occurs predominantly at sites of new bone formation (23), and thus it is thought to be dependent upon osteoblastic activity (25). In fact, significant correlation has been found between WBR and both biochemical (27, 29, 33–35) and histomorphometric indices of bone formation (35). Some investigators also reported retention values being closely related to urinary HOP/Cr excretion (24, 27, 29, 34), an index of bone resorption. Our data are in agreement with these observations, showing high correlation between WBR and both OC and HOP/Cr, thus confirming the validity of WBR as estimate of skeletal turnover.

All three biochemical markers of bone remodeling studied in this investigation (WBR, OC, and HOP/Cr) were significantly higher in the osteoporotic than in the normal population (Table I). Only serum OC in the Anova analysis was just below the significance level. These data, which confirm earlier reports, wherein bone turnover was measured by calcium kinetics (21), WBR (29), serum OC levels (36–39), or histomorphometric analysis of bone biopsies (40, 41), suggests that in a

Table VI. Effect of 1-yr Treatment with sCT on Three Markers of Bone Turnover in Postmenopausal Osteoporotic Women

Variable	Treatment	HTOP	NTOP	Pooled
WBR (*% injected dose*)	Before	42.0±4.0 (16)	29.3±4.3 (34)	33.4±7.3 (50)
	After	36.2±3.6*	27.4±2.9*	30.2±5.2*
Osteocalcin (*ng/ml*)	Before	11.46±5.91 (17)	5.86±2.12 (36)	7.65±4.55 (53)
	After	7.26±2.56*	4.61±1.11*	5.46±2.10*
HOP/Cr (*mg/g*)	Before	28.5±8.7 (17)	15.6±5.1 (36)	19.8±8.8 (53)
	After	22.2±7.1*	14.3±4.2‡	16.8±6.4*

Data are mean±SD. The number of patients for each group is given in parentheses. * $P < 0.001$. ‡ $P = 0.014$ before vs. after (Student's t test for paired data).

nonselected postmenopausal osteoporotic population the average rate of bone turnover is higher than in premenopausal or age-matched normal women. However, average values of biochemical parameters obtained in nonselected populations probably do not provide enough information on the cellular mechanisms responsible for such a heterogeneous condition.

We were unable to find any correlations between BMC (measured either at the lumbar spine or at the femoral diaphysis) and markers of bone turnover. Patients with HTOP had, as expected, higher levels of serum OC and urinary HOP/Cr; nevertheless their bone mass was not significantly lower than that of NTOP women. Furthermore, multivariate analysis of data revealed that only years elapsed since menopause was significantly correlated to bone density of the lumbar spine, and accounted for about 40% of vertebral BMC variability in the final model, elaborated by stepwise regression analysis. None of the parameters of bone turnover furnished substantial contribution to bone mass variability, indicating that measurement of these biochemical indices of bone remodeling does not predict the severity of bone loss after menopause.

Contrary to this observation, in an early report, Fogelman et al. (24) found a good correlation between WBR and rate of bone loss in oophorectomized women. Moreover, cross-sectional studies showed some degree of correlation between serum OC and bone density in postmenopausal women (37, 38). This finding has been recently confirmed by a prospective study of Slemenda et al. (39), indicating that higher rates of bone turnover can be associated with more rapid bone loss in postmenopausal osteoporosis. There is a possible explanation for the apparent discrepancy of our data with these findings.

In the years immediately following natural or artificial menopause a sharp loss of vertebral bone mass occurs (42–44), while bone turnover increases (21). In general, a reduction of bone mass would depend on both the imbalance between formation and resorption (45) and on how long the inefficient coupling lasts. Although it is not yet established whether, in a later phase of menopause, the rate of spinal bone loss slows down (43, 44) or remains constant (46, 47), it is conceivable that if an even balance between the bone remodeling processes is restored, this will occur by either an increase in bone formation or a decrease in bone resorption. This would lead to clinical pictures of reduced bone mass associated with either high, normal, or low bone turnover, thus implying that bone density will not be predicted by assessment of bone remodeling. The present study, in agreement with a recent report of Thomsen et al. (48), seems to confirm this hypothesis, indicating that although rates of bone remodeling can be related to rates of bone loss, a single determination of biochemical estimates of bone turnover cannot predict the degree of bone loss in a wide postmenopausal osteoporotic population.

Determination of WBR in our patients revealed that 32% of them had a bone turnover rate higher than normal women. These data are in good agreement with previous studies based on histmorphometric analysis of iliac crest bone biopsies, in which part of the patients were reported as having high or active bone remodeling rates (1–3, 14). The proportion of these cases compared with the whole osteoporotic population varies among the different studies, mainly because of the different criteria used in defining high bone turnover in histologic sections. All these reports, however, identify a subpopulation of postmenopausal osteoporotic women with an active remodeling disease. Unfortunately, with the data available to date, all obtained in cross-sectional studies, it is not possible to establish whether the enhanced bone remodeling detectable in this subset of osteoporotic subjects represents a selected population with a particular form of the disease, or is suggestive of a longitudinal heterogeneity of the disorder, expressing phases of different bone remodeling rates at different times.

Although assessment of bone turnover can be disappointing as a screening method to predict bone loss in postmenopausal osteoporosis, it can be useful for the choice of the pharmacologic treatment, as suggested by the second phase of our study. If the 53 patients were considered as a whole group, an increase of spinal BMC was observed after sCT therapy. However, when the subjects were divided according to bone turnover, there was a clear dissociation of effect (Fig. 2). The remarkable improvement of bone mass observed in HTOP patients, compared to NTOP women, demonstrates that sCT is indeed more effective when bone remodeling is more active, so that an inhibition of bone resorption is particularly useful. The stability of vertebral BMC in NTOP subjects is probably to be seen as a protective effect from a further bone loss that pre-

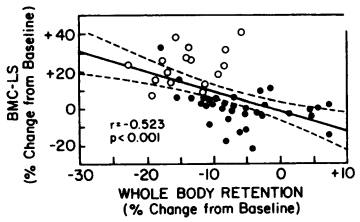

Figure 3. Correlation of changes in BMC at the vertebral bodies and changes in WBR (in percent from time 0) in 50 patients with postmenopausal osteoporosis, after 1 yr treatment with sCT. ○, HTOP; ●, NTOP.

sumably these patients would have experienced without treatment.

The extent of increase in bone mass that we observed at one year of treatment in HTOP patients is quite consistent (22%). This figure becomes much less impressive when data from all 53 patients are pooled (7%). The latter data is in good agreement with the 15% increase of total body calcium reported by Gruber et al. (7), and with the 13% increase of bone density at the distal radius observed by Mazzuoli et al. (8), using higher doses of calcitonin for one year. Our study extends these observations, showing that the effect of sCT on bone mineral content in an unselected postmenopausal population is almost entirely accounted for by a dramatic gain of bone mineral that occurs in patients with HTOP. In keeping with this finding is an early study by Wallach et al. (6), who reported a mean increase of 9% in total body calcium in 50% of osteoporotic patients treated with porcine calcitonin for more than one year. The other 50% did not respond to the therapy. A possible explanation for this observed variability of results, as the authors speculate, may be that the responders had elevated bone remodeling rates, and thus achieved a better result from calcitonin treatment.

Consistent with our previous observations in patients treated with estrogens (30), a dissociation of calcitonin effect was also evident between the two skeletal sites where bone density measurements were made. In contrast to the sCT effects in the lumbar spine, no improvement was found at the femoral shaft when the 53 patients were considered as a whole group. However, even in this case the HTOP group showed a better response to sCT treatment, with no changes in bone mass, compared with the substantial bone loss in the NTOP group. Thus, in HTOP, CT appears to be beneficial primarily at a skeletal site that is mostly involved in the bone loss occurring after menopause (46).

Also, in analogy with estrogens (21, 24, 30), the positive effect of sCT on bone mass was associated to a depression of bone turnover, as demonstrated by both the decrease of WBR and the high correlation between the percent changes of spinal bone mass and changes of WBR, observed after one year of therapy. The primary event induced by calcitonin was probably an inhibition of bone resorption, reflected by the decrease of HOP/Cr, an effect that has been previously documented by either a reduction of bone resorbing surfaces in iliac crest biopsies (7, 14), or a decrease of urinary hydroxyproline excretion (5, 8, 11). Inhibition of bone resorption ultimately leads to a depression of bone formation, due to the coupling phenomenon (49, 50). This might explain the decrease of serum OC observed in our patients. However, since calcitonin therapy results in an increment of bone mass in HTOP, it is conceivable that in this case the drug acts by uncoupling the bone remodeling processes, thus causing bone formation to prevail; at least during one year of treatment.

In conclusion, the present investigation demonstrates that assessment of bone remodeling rates by a single determination of either biochemical parameters, such as osteocalcin and urinary hydroxyproline, or bone-seeking radioisotopes distribution (WBR), cannot help predict the degree of bone loss in postmenopausal osteoporosis, but it can be useful as diagnostic tool in selecting the proper therapeutic approach. The good correlations between the biochemical parameters and the retention values suggest that all of them can be used to diagnose high-turnover osteoporosis, and thus identify those postmenopausal osteoporotic women who may benefit from treatment with calcitonin.

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