1995

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Mario Caniggia
University of Siena, Italy

Bruno Frediani
University of Siena, Italy

Leonardo Osti
University of Siena, Italy

Utah State University
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HIP PROSTHESES AND BONE MINERAL ABSORPTIOMETRY: EFFECT OF SHORT-TERM ADMINISTRATION OF CALCITRIOL

Mario Caniggia[1,*], Bruno Frediani[2] and Leonardo Osti[1]

[1]Institute of Clinical Orthopedics, University of Siena, Italy
[2]Centre for the Study of Endocrine and Metabolic Diseases of the Skeleton, University of Siena, Italy

Abstract

In this double blind study, seven out of fourteen patients who had received a cementless hydroxyapatite-covered hip prosthesis were given calcitriol (1 μg daily), and seven an inert placebo for a period of four months. At the end of this period, total body bone densitometry (TBBD) and absorptiometric measurements in the regions of interest (ROIs) close to the prosthesis and in the opposite femur revealed that the TBBD values had decreased in the patients receiving placebo and increased in those receiving calcitriol. Furthermore, bone mineral density in the ROIs had increased on the non-operated side of the calcitriol-treated patients (although to a lesser extent in the calcitriol-treated group).

Key Words: Hip prosthesis, periprosthesic bone resorption, total-body bone absorptiometry, calcitriol treatment.

*Address for correspondence:
Mario Caniggia
Istituto di Clinica Ortopedica,
Università degli Studi di Siena,
Ospedale "Le Scotte",
Viale Bracci,
53100 Siena, Italy
    Telephone number +39 (577)-936337, or 48336
        FAX Number +39 (577)-280774

Introduction

The lengthening of average life expectancy has led to an increase in the incidence of fractures of the femoral neck due to osteoporosis and the physiological reduction in bone mineral content. Another increasingly frequent disease is coxarthrosis due to age and increase in body weight. These pathological conditions often require the implantation of a hip prosthesis. The use of cementless hip prostheses has naturally reduced the incidence of the biological and mechanical alterations due to the cement itself [24], but their introduction has also led to stress shielding and the consequent remodelling of periprosthetc femoral tissue [1, 19, 20, 38]. This remodelling is caused by various factors, some of which are related to the prosthesis (its design, the modulus of elasticity of the material, and the presence and extent of micro and macroporous surfaces) [18], and others to the patient (age, body weight, systemic or regional osteoporosis, physical activity and bone ingrowth). Periprosthetc osteoporosis may lead to implant movement but does not appear to alter the possibility of adequate bone ingrowth [1, 18]. When a cementless prosthetc implant in either porotic or normal bone is being considered, the important factors are the choice of the prosthesis (which must guarantee sufficient elasticity and ensure an adequate press-fit on the bone), its structural material (titanium) and any coating it may have (such as hydroxyapatite) [1].

Periprosthetc bone loss can be verified by using conventional radiology [18, 24] and/or densitometry. The first method provides a morphological description and allows any implant defects to be evaluated, but it cannot be used to monitor bone density over time because of its inability to detect bone density variations of less that 30-40% [23, 27]. Bone densitometry by means of dual photon absorptiometry (DPA) or dual X-ray absorptiometry (DXA) is the most accurate and precise method for studying bone mass [3, 32, 35, 34], and has been used in a number of studies to measure periprosthetic bone loss [1, 20, 25, 26, 33, 37]. In these studies, the periprosthetic areas have been subdivided in
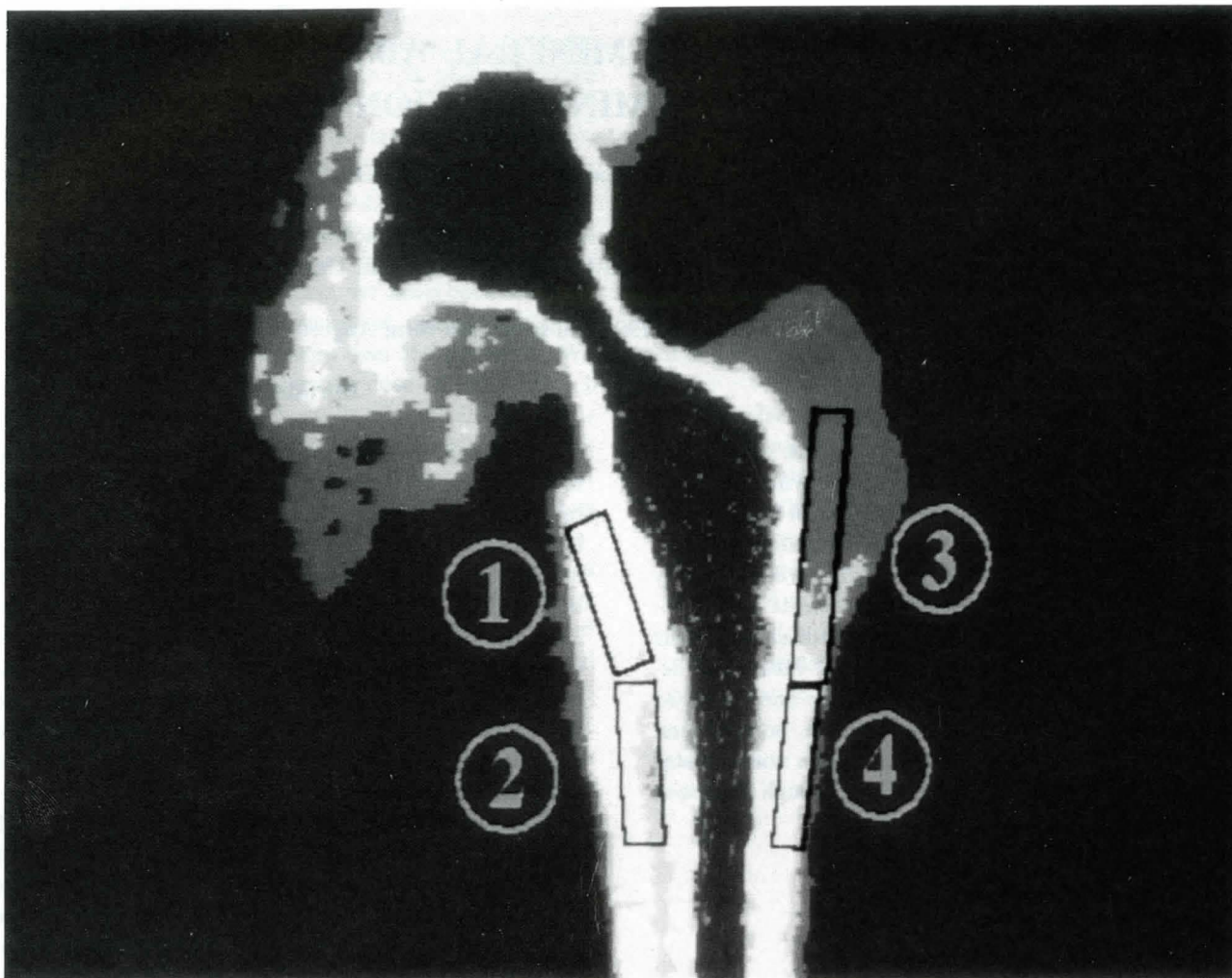
Figure 1. DXA visual display of proximal femur: location of the four regions of interest.

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various ways, the *in vivo* reproducibility in the studied regions ranging from 2% to 7% [25, 26, 33, 37, 40]. An accurate and precise evaluation of bone mass density (BMD) in the regions of interest (ROIs) of the limb with a prosthesis, when compared with those of the contralateral limb, can provide indications concerning local bone remodelling and predict the success and durability of the implant [2, 12, 13, 15, 16, 31, 36]. Depending on the time at which the measurements were made and the analytical techniques used, absorptiometry investigations of periprosthetic regions have documented a more or less evident demineralization [1, 20, 25, 33]. Kilgus *et al.* [25] measured bone density in six medial and six lateral regions around the prosthesis: 5-7 years after the operation, in comparison with controls, they found that: (a) there was a reduction in BMD of 20.2% in the region containing the lesser trochanter, and of 25.5% in the region below it; (b) the greatest reduction in BMD was in the region above the lesser trochanter

(34.8%); and (c) the reduction in BMD was always less in the distal regions. Engh *et al.* [18] measured bone density post mortem by subdividing the prosthetic part of the femur into three equal areas and then comparing them with the corresponding contralateral areas; the largest reduction in mineral content (45%) was observed in the proximal third. McCarthy *et al.* [33] analysed two regions and, three years after the operation, showed: (a) a 40% mineral loss in the region containing the lesser trochanter, and (b) a 28% loss in the distal region. More than 7 years after the operation, the losses were respectively 40% and 49%. Kiratli *et al.* [26] studied four ROIs one year after the operation, and found that the greatest mineral loss was in the region of the lesser trochanter (32.6%) and in the regoin immediately below it (30.3%). Trevisan *et al.* [40] studied seven periprosthetic regions and compared them with the contralateral regions of the healthy femur; eighteen months after the operation, they found the greatest

reduction in BMD in the proximal and medial region (Z score: approximately 1.8) and in the greater trochanter (Z score: approximately 1.4).

At physiological doses of 1 μg/day, synthetic 1,25(OH)2vitD3 (calcitriol): (a) normalizes the intestinal absorption of calcium in patients with postmenopausal osteoporosis [4, 9]; (b) eliminates bone mineral losses [9, 10]; (c) reduces the incidence of fractures [9, 10, 11, 29]; (d) leads to an increase in osteocalcin [7], an index of osteoblastic activity; and (e) has no toxic side effects provided patients are not given calcium supplementation [9].

The dual aims of this study were: (a) to measure the BMD in the total body, in the operated limb, in the contralateral limb, and in four periprosthetic ROIs; and (b) to evaluate the efficacy of 1,25(OH)2vitD3 on bone loss in the same districts at the time of a prosthesis implantation and four months later. Our study differed from previous studies in that it evaluated bone mineral measurements immediately after the implantation of the hip prosthesis, as well as the effect of four months of calcitriol treatment.

Material and Methods

Patients

Fourteen subjects were studied: four males (aged 58-80 years), and ten females (aged 61-90 years). Nine of the patients (3 men and 6 women) underwent hip implantation as a result of fractures of minimal cause in senile or postmenopausal osteoporosis; the remaining five (1 man and 4 women) underwent total hip replacement because of coxarthrosis. Positive diagnoses were made on the basis of the patients' histories (fractures, pain, spine deformities), X-rays (demineralization, fractures), densitometry of the entire body and the femoral area, laboratory data (plasma calcium, phosphate and alkaline phosphatase levels; 24 hour urinary calcium, phosphate and hydroxyproline excretion). Patients with secondary osteoporosis were excluded. A titanium Omnifit prosthesis (Osteonics) with a hydroxyapatite coating was used in all of the patients.

Of the 14 patients seven were treated with calcitriol (1 μg/day), without any calcium supplementation, from the fifth day following the operation, whereas seven others received two inert placebo tablets per day. This was a double blind study, with the patients being randomly allocated to the two groups. All of the patients gave their informed consent.

Methods

The densitometric investigations were performed by means of Lunar DPX equipment, using a constant potential X-ray source coupled to a "K-edge" filter in such a way as to obtain two photon energy levels (one of 40, and the other of 70 keV). Five days after the operation, and after four months of treatment, each patient underwent three absorptiometric scans: (a) one of the entire body; (b) one of the proximal femur on the operated side; and (c) one of the proximal femur on the contralateral side. Of the total body scans, the following absorptiometric analyses were considered: (a) the total skeleton; (b) the operated limb; and (c) the non-operated limb. For the total body and the individual anatomical regions evaluated, absorptiometry provided: (a) the values of bone mineral content in grams (BMC); and (b) the values of bone mineral density in g/cm^2 (BMD). The "*in vivo*" precision, calculated as the coefficient of variation (CV%), was less than 1% for total body BMD [35] and less than 1% for the BMD of operated and non-operated lower limbs.

For the post-operative comparison, four ROIs at the upper end of the femoral diaphysis were identified for both the operated and the contralateral sides. These regions, indicated by the numbers 1, 2, 3, and 4 in Figure 1 were: (a) region 1, defined as being "of the lesser trochanter", was 5-10 mm wide and 20-30 mm long; (b) region 2, immediately below region 1 (in the medial femoral diaphysis), was 5-10 mm wide and 20-30 mm long; (c) region 3, defined as being "of the greater trochanter", was 5-10 mm wide and 25-35 mm long; and (d) region 4, immediately below region 3 (in the lateral femoral diaphysis) was 5-10 mm wide and 20-30 mm long. The reproducibility of the measurements (CV%) for each periprosthetic region was calculated in five subjects by scanning the prosthesis and the contralateral femurs twice on the same day, with the patients being repositioned between scans. The CV% was between 2.09% and 4.89% for the limb with the prosthesis, and between 1.26% and 3% for the opposite limb. In each individual case, a comparison was made between the ROIs of the operated femur and those of the opposite femur.

Before the operation, and on a monthly basis after the operation, the following parameters were measured in all of the patients: plasma calcium (using atomic absorption spectrophotometry; Perkin-Elmer model 2280), plasma phosphate and serum alkaline phosphatase (using standard methods) The last check was made four months after treatment.

Statistical evaluations

The densitometric data were expressed as means ($\pm$ standard deviation, SD) and per cent variations. The Student's t-test for unpaired data was used to evaluate the significance of the difference between the mean values and the percentage variations of the two treatment groups, and of the prosthesis and contralateral femur.

Table 1. Mean BMD values ($\pm$ SD) and per cent variations of the total body, the entire prosthetic leg and the entire opposite leg, before and after four months of treatment with placebo or calcitriol.

	Placebo Group (BMD g/cm^2)				Calcitriol Group (BMD g/cm^2)			
	Baseline	Final	% var	P	Baseline	Final	% var	P
Total body	0.942	0.930	-1.38	n s.	0.920	0.922	0.176	n.s.
	(0.132)	(0.141)	(2.143)		(0.082)	(0.086)	(1.374)	
Prosthesis leg	0 960	0.901	-6.486	< 0.05	0.918	0.883	-3.601	n.s.
	(0.156)	(0.176)	(5.214)		(0.124)	(0.124)	(6.385)	
Opposite leg	0.931	0.922	-1.220	n.s.	0.972	0.962	-0.921	n.s.
	(0.243)	(0.252)	(1 931)		(0.183)	(0.175)	(1.281)	

Table 2. Mean BMD values ($\pm$ SD) in the four regions of interest of the operated and non-operated femur, before and after four months of treatment with placebo or calcitriol.

Regions of Interest	Placebo Group (BMD g/cm^2)			Calcitriol Group (BMD g/cm^2)		
	Baseline	Final	P	Baseline	Final	P
Prosthesis side						
1	1.353 $\pm$ 0.538	1.043 $\pm$ 0.652	< 0.05	1.467 $\pm$ 0.460	1.311 $\pm$ 0.467	n.s.
2	1.401 $\pm$ 0.701	1.180 $\pm$ 0.747	< 0.05	0.958 $\pm$ 0.335	0.947 $\pm$ 0.371	n.s.
3	0.766 $\pm$ 0.276	0.535 $\pm$ 0.423	< 0.05	0.668 $\pm$ 0.311	0.492 $\pm$ 0.301	n.s.
4	1.164 $\pm$ 0.332	0.934 $\pm$ 0.467	n.s.	1.361 $\pm$ 0.378	0.943 $\pm$ 0.218	< 0.05
Opposite side						
1	1.480 $\pm$ 0.661	1.349 $\pm$ 0.668	n.s.	1.456 $\pm$ 0.407	1.509 $\pm$ 0.381	n.s.
2	1.421 $\pm$ 0.792	1.420 $\pm$ 0.852	n.s.	1.152 $\pm$ 0.244	1.252 $\pm$ 0.298	n.s.
3	0.754 $\pm$ 0.456	0.712 $\pm$ 0.508	n.s.	0.705 $\pm$ 0.305	0.799 $\pm$ 0.274	n.s.
4	1.193 $\pm$ 0.551	1.146 $\pm$ 0.576	n.s.	1.518 $\pm$ 0.453	1.517 $\pm$ 0.355	n.s.

The significance of the mean values before and after treatment was evaluated using the t-test for paired data.

Results

Table 1 shows the mean BMD values and % variations for the entire body, the prosthesis limb and the opposite limb, before and after treatment with placebo or calcitriol. The BMD values in the operated limb were significantly lower after four months of placebo treatment (0.960 versus 0.901; p < 0.05; -6.1%), but the reduction after calcitriol treatment was not significant (0.918 versus 0.883; p: not significant, n.s.; -3.8%).

Table 2 shows the mean BMD values in the four ROIs in the operated and opposite limbs, before and after placebo or calcitriol treatment. After four months of placebo therapy, the BMD values in regions 1, 2 and 3 were significantly lower in the prosthesis limb, but there was no significant reduction in the opposite limb. However, after four months of calcitriol treatment, the BMD values in regions 1, 2 and 3 of the operated limb were not significantly lower, but those in region 4 had significantly decreased. In the opposite limb, the mean values in the same regions had increased, although not significantly so.
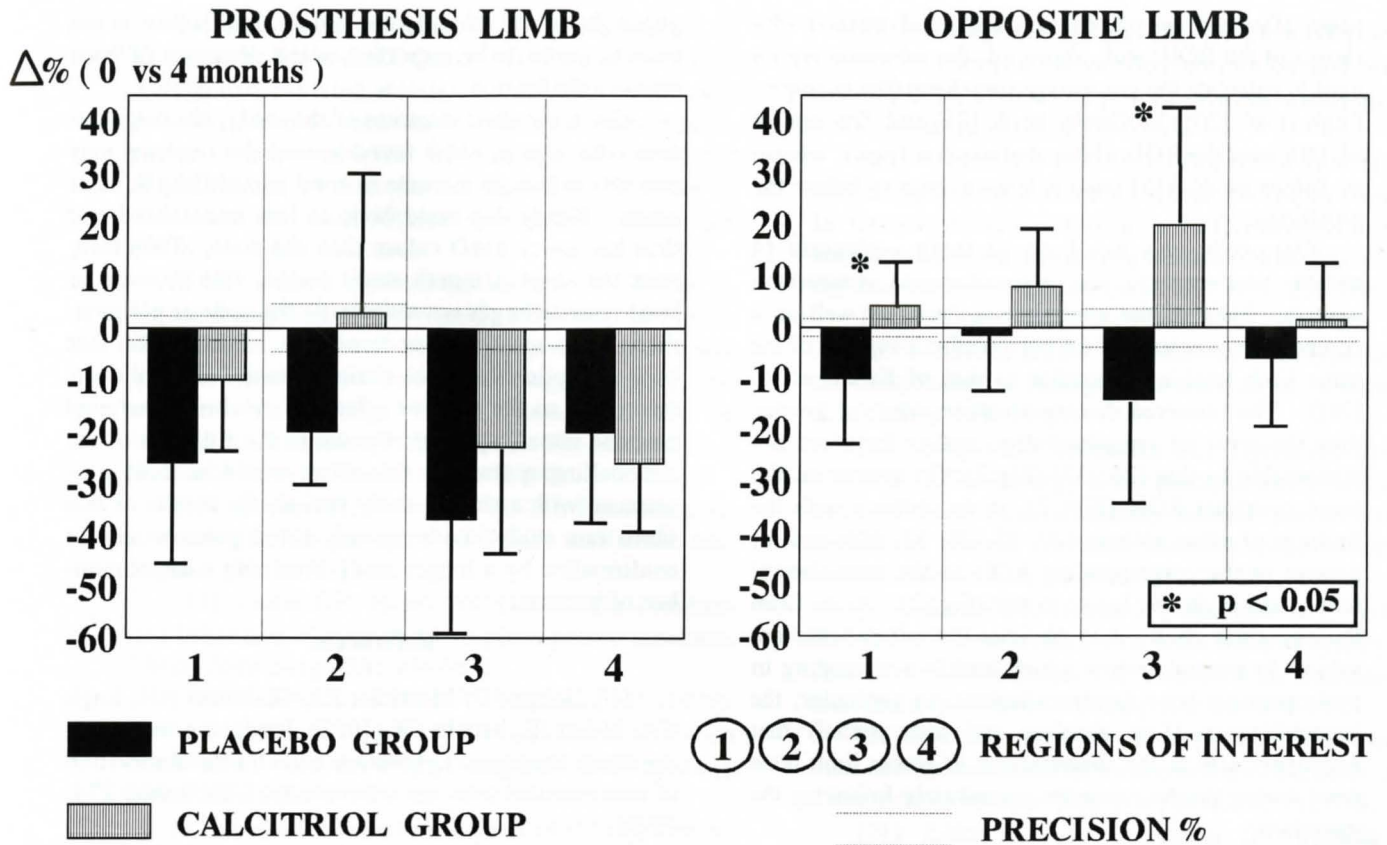
PROSTHESIS LIMB

Δ% (0 vs 4 months)

OPPOSITE LIMB

PLACEBO GROUP

CALCITRIOL GROUP

(1)(2)(3)(4) **REGIONS OF INTEREST**

PRECISION %

Figure 2. Percentage variations ($\pm$ SD) in BMD in the four regions of interest of the operated and contralateral femur after four months of treatment with placebo or calcitriol.

Figure 2 shows the percentage variations in the BMD of the four ROIs, before and after placebo or calcitriol therapy. In the operated limb, the percentage decrease in BMD after calcitriol therapy was lower than in the subjects treated with placebo, although the differences between the percentages did not reach statistical significance. In the non-operated limb, there was a decrease in BMD in the placebo group and an increase in the calcitriol group. The difference between the percentages were not significant in the placebo group, but they were in regions 1 and 3 of the group treated with calcitriol. The plasma calcium and phosphate levels, as well as the serum alkaline phosphatase values, were normal in all patients before surgery, and did not change after treatment with either calcitriol or placebo.

Discussion

Osteoporosis is a reduction in bone mass with normal mineralization of the bone matrix and a microarchitectural deterioration in bone tissue, with a consequent increase in bone fragility and greater susceptibility to fractures. Total body absorptiometry is a very good method for measuring bone mass in osteoporosis, and it also allows monitoring in both non-treated and drug-treated patients [32, 35].

In previous studies involving osteoporotic patients, we have shown the long-term effects of calcitriol in eliminating bone losses throughout the entire body [9, 10, 11]. Although a period of four months is usually considered to be insufficient to reveal significant variations in BMD, regional analysis of the entire operated limb and the entire opposite limb in the patients participating in the present study showed: (a) a significant reduction in the BMD of regions 1,2 and 3 in the prosthesis limb in the placebo group; (b) no significant reduction in the patients treated with calcitriol in the same regions, but a significant decrease in region 4. A study of the mineralization of the periprosthetic ROIs showed the presence of clear demineralization around the prosthesis.

The results reported by other authors vary according to the time of observation (from one to seven or more

years after the operation), the analytical method (the choice of the ROIs) and, above all, the reference region used to calculate the percentage variations (for example, Engh *et al.* [20], McCarthy *et al.* [33] and Trevisan *et al.* [40] used the ROIs of the contralateral femur, whereas Kilgus *et al.* [25] used a femoral region below the prosthesis.

Our study was based on an early evaluation (4 months post-surgery), and a simultaneous comparison with the ROIs of the contralateral limb, as well as a comparison over time of the periprosthetic regions of the same limb (making it similar to that of Kiratli *et al.* [26]). The observed demineralization was: (a) greater than the error of reproducibility, and is therefore not attributable to that [26, 37] (Fig.2); (b) greater in the more proximal ROIs (Fig. 2), in accordance with the findings of other authors [20, 25, 26, 33, 40]; and (c) present in the corresponding ROIs in the contralateral femur, although to a lesser extent (Fig. 2). Aside from the operation itself, it is obvious that all patients are subject to general factors which lead to a worsening in post-operative bone demineralization: in particular, the immobilization (first absolute and then partial) that negatively affects the maintenance of lower limb bone mass during the four months immediately following the operation.

It has been shown that long-term treatment with calcitriol (1 μg/day) has a beneficial effect in postmenopausal osteoporosis [5, 6, 8, 24, 17, 21, 22, 29, 30, 39]. In terms of total body absorptiometry, this treatment is capable of countering the progressive decrease in bone mineral density, which is well known in osteoporotic women who are not appropriately treated. It is clear that calcitriol treatment was expected to be equally efficacious in the patients participating in the present study, and this was confirmed by the increased densitometric values in the ROIs of the non-operated limb, as well as by the lower bone loss observed in the ROIs of the operated limb (Fig. 2).

Osteoblasts produce both bone collagen, the most important component of the organic bone matrix, and osteocalcin, or Bone G1a Protein, which is quantitatively the second largest protein component of the skeleton. It is well known that 1,25(OH)2vitD is indispensable for the production of osteocalcin by osteoblasts, and it has been shown that calcitriol leads to a systemic increase in plasma osteocalcin [7]. Recent studies [28] seem to show that, in comparison with control subjects, there is a reduction in 1,25(OH)2vitD in the bone tissue of osteoporotic patients with hip fracture. The use of calcitriol in postmenopausal osteoporosis may achieve two goals: (a) that of normalizing intestinal calcium absorption, and thus blocking progressive bone loss; and (b) that of increasing the production of osteocalcin which,

although its real physiopathological significance is not known, seems to be important in the processes of bone matrix calcification.

Given the short duration of the study, the considerable reduction in BMD found around the implants may partially reflect an increase in bone remodelling in these areas. Newly deposited bone is less mineralized and thus has lower BMD values than old bone. Therefore, over the short 4 month study period, this increase in bone remodelling is not necessarily the same as periprosthetic bone resorption or bone loss. It is known that bone resorption decreases during chronic calcitriol treatment, and so the positive effects of calcitriol treatment on bone mass may be partly due to the filling in of the remodelling space. As this effect would be more pronounced with a shorter study period, the results of this short-term study involving only a few patients require confirmation by a longer study involving a larger number of patients.

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Discussion with Reviewers

Reviewer V: Could not the difference in BMD baseline values between groups be a cause of statistical difference between treated and control groups?

Authors: The number of patients in the present paper is too few for a meaningful statistical analysis. Nevertheless, the differences of the results in placebo group versus the calcitriol group was significant when the mean baseline values were either higher or lower in the single regions of interest. For example, for region 1: 1.353 versus 1.043 and 1.467 versus 1.311; and for region 2: 1.401 versus 1.180 and 0.958 versus 0.947.

R.G. Erben: With a patient number of 7 per group, would a non-parametric test not be more appropriate for statistical evaluation?

Authors: Non-parametric text could be more appropriate for statistical evaluation though the resulting outcome will be substantially similar.

W.S.S. Jee: Could you speculate why region 4 in the calcitriol group showed a decrease in BMD?

H.U. Bryant: In region 4, there seems to be a significant decrease in BMD in the calcitriol group but not so in the placebo group. This data would seem to go against the hypothesis of the authors and is not consistent with the results from the other sites. Is this the result of a redistribution phenomenon?

Authors: We do not know why region 4 showed a decrease in BMD in the calcitriol group. As the study is continuing and a new steady state is at one year of treatment, it is possible that this decrease in region 4 will not persist.

R.G. Erben: In the early phase of calcitriol treatment, serum and urinary calcium levels should be measured more frequently in order to exclude development of hypercalcemia/hypercalcuria. Do you have data on calcium excretion, which is the most sensitive marker for calcitriol toxicity?

Authors: During the early phase of calcitriol treatment, we usually measure bone metabolism parameters on a monthly base.

W.S.S. Jee: Do you have any histological material that would clarify how this those of calcitriol is acting on the tissue level?

Authors: We do not have any histological data that would clarify how calcitriol acts at the tissue level.