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MEASUREMENT OF TOTAL BODY CALCIUM IN OSTEOPOROTIC PATIENTS TREATED WITH SALMON CALCITONIN

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In the past, the evaluation of therapies for osteoporosis has been limited by the lack of a suitable quantitative end point. The introduction of the technique of in vivo total body neutron activation analysis (TBNAA) has made possible the precise and accurate measurement of total body calcium (TBCa). Since almost 99 percent of TBCa is in the skeleton, TBNAA gives a direct measurement of skeletal mass. Thus, changes in skeletal mass serve as an objective criterion in the evaluation of the efficacy of the therapy in osteoporosis (1).

Studies performed at Brookhaven National Laboratory (2-4) and elsewhere (5) have reported the use of calcitonin (CT) in the treatment of primary osteoporosis and related conditions in a limited number of patients. The physiological effects of CT as an inhibitor of bone resorption has been the rationale of its use.

The results of a randomized, controlled, 2 year therapeutical trial of CT in a group of postmenopausal osteoporotic women are presented in this report. All patients were Caucasian females of 50-75 years of age, who had sustained one or more vertebral compression fractures but were ambulatory. At the beginning of the study, patients were hospitalized and screened for evidence of osteopenia from sources other than postmenopausal osteoporosis. All patients signed an informed consent form and the study was approved by the institutional review committee.

Thirty-four of these patients were allocated at random to a treatment group receiving daily 100 MRC units of synthetic salmon CT, (Calcimar, Armour) subcutaneously, daily and oral calcium (calcium carbonate, 600 mg twice daily) or to a control group receiving the calcium. Both groups also received one multivitamin capsule, containing 500 I.U. of vitamin D per day. The therapy was continued for 2 years, with serial clinical and laboratory follow-up every 4-6 weeks. X-rays of the dorsolumbar spine were obtained at baseline, and at one and 2 years, and were evaluated blindly by a radiologist.

Nine of the patients failed to complete the full program therapy and data on one patient was invalid because of interfering disease.

Thus the effects of CT were evaluated in 24 osteoporotic women (10 in the CT group and 14 in the control group). The summary of the initial clinical features and laboratory measurements of the patients is presented in Table I. Comparison of these parameters in each group revealed no significant differences between the CT group and control group.

Skeletal mass was evaluated by the measurements of TBCa by TBNAA and as bone mineral content (BMC) of the distal radius (8 cm site) by photon absorptiometry with a Norland instrument. Details of these techniques have been previously published (1). These measurements were performed every 6 months.

The percent of change in TBCa from baseline during the period of treatment is shown in Fig. 1. The maximum increase in TBCa (5% ± 1.8 SE) was observed at one year in the CT group; at that time the control group had lost 1% ± 1.76 of TBCa. The difference between these two values of the CT group vs. control group was statistically significant by a t-test ($p < 0.05$). At the end of two years, the TBCa had increased by 2.14% ± 1.6 in the CT group, whereas the TBCa in the control group had decreased by 2.1% ± 0.9. The difference between these two

values was also significant ($p < 0.05$). A regression analysis of these percent changes of TBCa values showed a significant difference between the two groups ($p < 0.05$). Moreover, the average slopes of the absolute values of these two groups, 0.470 ± 0.414 SE for the CT group and -0.595 ± 0.225 for the control group, were significantly different when compared ■ ($p < 0.02$). This difference was also manifested when the adjusted differences of the TBCa values were compared to the mean of the observations.

There was no significant difference in the BMC of the radius between the two groups during the study. Table II shows the progression of vertebral fractures and the incidence of new vertebral compression fractures. No significant differences in these two aspects were observed between the two groups. However, a slight trend to fewer new compressions in the CT group was observed, particularly during the first year of treatment.

The changes in laboratory measurements at the end of the treatment as compared to baseline are summarized in Table III. No significant changes were detected in plasma calcium and alkaline phosphatase in either group of patients. In the CT group there was a small, but significant decrease in plasma inorganic phosphorus value from 3.5 mg/dl ± 0.08 SE to the 3.1 ± 0.09, ($p < 0.05$) and an increase in urinary calcium excretion from 133 mg ± 15 per 24 hours to 177 ± 22, ($p < 0.05$). In this group, however, the urinary calcium corrected by creatinine did not increase significantly. In the control group, on the other hand, the urinary calcium corrected by creatinine decreased significantly from 158 mg/g ± 18 SE per 24 hr to 136 ± 17, ($p < 0.025$). The changes observed in the CT group are compatible with the values calculated on the basis of the action of CT. CT should stimulate the parathyroid secretion and produce a decrease in plasma phosphorus and an increase in the calcium absorbed in the intestine. This action is

related to an increase in 1,25-dihydroxy cholecalciferol, which also leads to an increase in urinary calcium. A possible direct effect of CT, however, producing a decrease of plasma phosphorus and an increase in urinary calcium has also been postulated (6,7).

Two patients died of diseases unrelated to their osteoporosis during the study; both were in the control group. Side effects, chiefly transient nausea or irritation at the site of the injections, were noticed in the 15 of the 17 patients originally enrolled in the CT group. The CT was discontinued in 4 patients because of the side effects considered related to the injections. One additional patient discontinued the CT because of depression, and another refused to continue with injections after presenting a seizure; this last patient was receiving anti-convulsants at that time. Only one of the patients receiving CT developed antibodies to salmon CT in significant titers and binding. This patient had a two percent decrease in her TBCa at two years of treatment as compared to baseline.

In conclusion, this study suggests that the long-term administration of salmon CT produces a modest but significant increase in TBCa in patients presenting with postmenopausal osteoporosis. On one hand, this increase in TBCa indicates a gain of cortical and trabecular bone. However, no increase was observed in the BMC of the radius of the CT treated patients - BMC measures cortical bone at the level of the radius. There is, therefore, the possibility that the gain in TBCa observed in treated osteoporotic patients may represent, in part, some gain in trabecular bone. Trabecular bone has been considered the predominant type of bone at deficit in osteoporosis, although the cortical vertebral frame may play a role in preventing compression fractures (8).

The decreased effectiveness of CT at 2 years of administration in these patients may limit the sustained gain in skeletal mass in prolonged treatments. However, the significant gain in the initial year is not without importance. This pattern of response raises the possibility of implementing a sequential therapy as an alternative complement to single agent treatment or to a combined therapy approach (9). Further studies on the mechanisms of action of CT and in the decreased effectiveness of CT after one year of therapy are warranted.

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TABLE I

OSTEOPOROTIC FEMALES WHO COMPLETED 2-YEAR EVALUATION

BASELINE CHARACTERISTICS (mean = SD)

	CALCITONIN (N = 10)	CONTROL (N = 14)	P*
Age (years)	64.1 ± 6.9	63.2 ± 7.6	NS
Height (M)	1.56 ± 0.07	1.57 ± 0.08	NS
Weight (K)	63.5 ± 6.3	56.2 ± 9.9	NS
Average # of Vertebral Compressions	5.1 ± 3.4	4.8 ± 3.3	NS
Severity Bone Pain (0 - 5)	2.10 ± 0.74	2.33 ± 0.98	NS
Mobility of Patient (0 - 5)	1.70 ± 0.95	2.17 ± 0.83	NS
Plasma Ca (MG/DL)	9.38 ± 0.18	9.41 ± 0.32	NS
Plasma P ('G/DL)	3.5 ± 0.3	3.4 ± 0.3	NS
Alkaline Phosphatase (IV/E)	72 ± 10	71 ± 28	NS
Urinary Ca (MG, 24 H)	115 ± 47	158 ± 66	NS
Urinary Ca/creatinine (MG/G, 24 H)	133 ± 47	196 ± 91	NS
Total Body Calcium (G)	616 ± 107	637 ± 106	NS

* T-TEST

TABLE II

INCIDENCE OF VERTEBRAL COMPRESSION FRACTURES

	DURING 1st YEAR		DURING 2nd YEAR	
	NO. OF PATIENTS	NO. OF FRACTURES/ PATIENT/YEAR	NO. OF PATIENTS	NO. OF FRACTURES/ PATIENT/YEAR
NEW COMPRESSIONS				
Calcitonin (N = 10)	1*	0.200 (2/10)	2**	0.400 (4/10)
Control (N = 14)	3+	0.375 (5/14)	2++	0.357 (5/14)
Fisher's Exact Text	NS	NS	NS	NS
WORSENING OF PREVIOUS COMPRESSIONS				
Calcitonin (N = 10)	1°	0.100 (1/10)	0	0.0 (0/10)
Control (N = 14)	2#	0.571 (8/14)	1##	0.143 (2/14)
Fisher's Exact Text	NS	NS	NS	NS

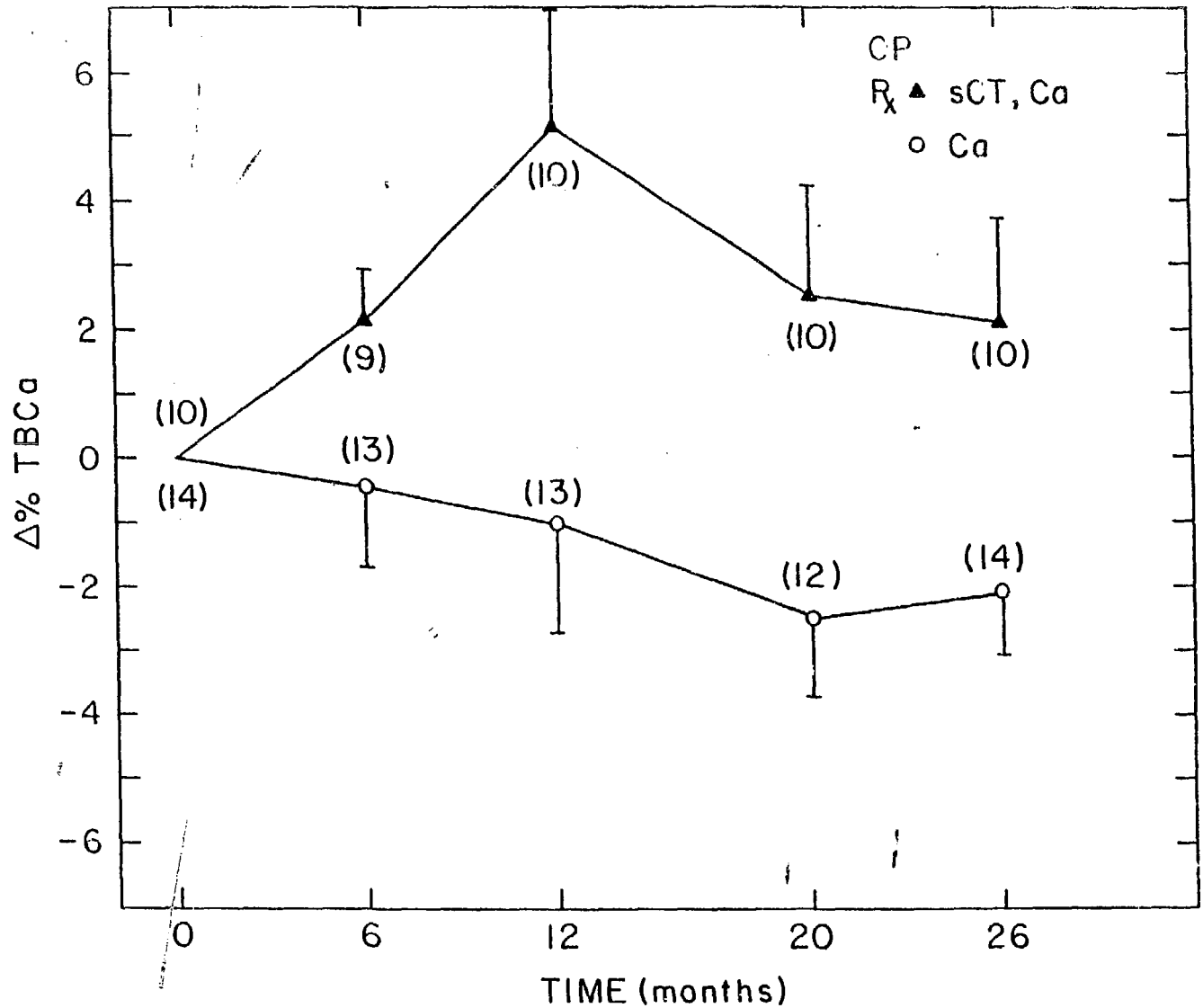
(*) One patient had 2 new compression fractures
(**) Two patients had 1 and 3 new compression, respectively
(+) Three patients had 1, 2, and 2 new compressions, respectively
(++) Two patients had 2 and 3 new compression fractures, respectively
(0) One patient had 1 worsening compression fracture
(#) Two patients with 3 and 5 worsening compressions, respectively
(##) One patient with 2 worsening compression fractures

TABLE III

MEAN CHANGES IN BIOCHEMICAL PARAMETERS

	BASELINE*	2 YEARS	P**
CALCITONIN (N = 10)			
C_{A_P} (MG/DL)	9.38 ± 0.06	9.23 ± 0.13	NS
P_P (MG/DL)	3.5 ± 0.08	3.1 ± 0.09	<0.001
Alkaline Phosphatase (IU/1)	72 ± 3	83 ± 5	NS
C_{A_U} (MG, 24 H)	133 ± 15	177 ± 22	<0.05
C_{A_U}/Creatinine$_U$ (MG/G, 24 H)	115 ± 15	134 ± 21	NS
CONTROL (N = 14)			
C_{A_P}	9.41 ± 0.09	9.25 ± 0.08	NS
P_P	3.4 ± 0.08	3.3 ± 0.08	NS
Alkaline Phosphatase	71 ± 7	68 ± 6	NS
C_{A_U}	196 ± 24	178 ± 29	NS
CA/Creatinine	158 ± 18	136 ± 17	<0.025

(*) = MEAN ± Standard Error of the mean
(**) = By dependent T-TEST
(N) = NUMBER OF PATIENTS


CP
Rx ▲ sCT, Ca
o Ca
Δ% TBCa
6
4
2
0
-2
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(9)
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(13)
(13)
(12)
(14)
0
6
12
20
26
TIME (months)

FIG. I