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OPTIMAL CALCIUM THERAPY

A Method Affording Subjective and Objective Improvements

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Since 1947, when Albright advanced the hypothesis that osteoporosis (postmenopausal and senile) is due to deficient production of bone protein the usual treatment for this disease has been administration of anabolic steroids. Although this usually leads to a subjective improvement in the patient's condition, there would seem to be no convincing evidence of an objective reduction in the osteoporosis. This situation has raised doubts as to the efficacy of hormone therapy and there has been a tendency to return to the former calcium treatment; this trend was no doubt promoted by the efforts of Nordin (1960, 1961) who, in a number of articles, has pointed to the close relationship between chronic dietary calcium deficiency and subsequent osteoporosis.

With the evolution of more exact methods for measuring the density of the skeleton, we have over a 2-year period (1968–69) been giving intensive intravenous calcium therapy, and performing simultaneous measurements of the bone density; both subjective and objective improvements have been recorded.

MATERIAL

From a regular orthopaedic out-patient clinic a number of patients suffering from radiologically confirmed severe osteoporosis were selected for admission and more intensive treatment. In most of the patients there was compression of the vertebrae, and all complained of severe symptoms.

Table 1. Sex and age distributions for the osteoporosis series.

	Number	Age (years)
Men	2	48, 61
Women	15	56, 57, 61, 62, 62, 63, 63 67, 68, 71, 71, 72, 72, 72, 75

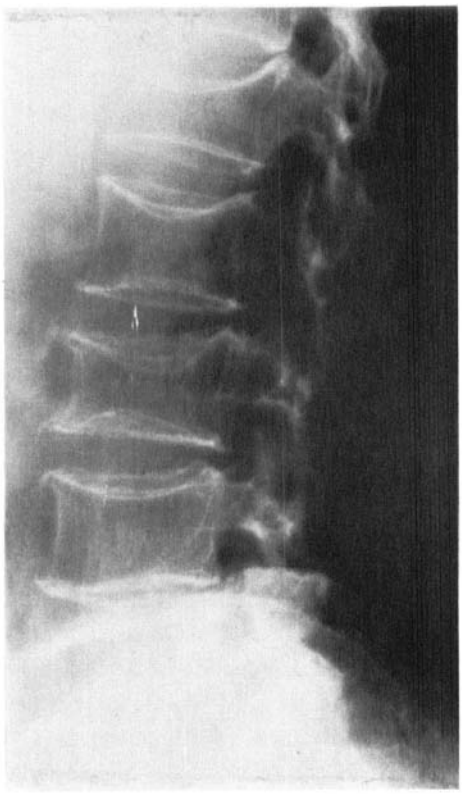

Figure 1. Radiograph of a patient with severe osteoporosis and compression of vertebrae.

Because the pain in osteoporosis is usually located in the back it is difficult to distinguish this disease from other back conditions eliciting similar symptoms. It is commonly considered that moderate osteoporosis in the spine is unaccompanied by pain, this appearing only when there is a compression fracture, and thus usually disappearing in a few months when the fracture has healed. On the other hand, it is obvious that in the case of severe vertebral osteoporosis symptoms are elicited that must inevitably be ascribed to this disease; they include a feeling of weakness of the back, and pain in the erect position and during loading of the spine; the patient feels the need to support himself on his arms, and has to rely on a corsette; considerable relief is obtained in the horizontal position, and for this reason the patient sometimes prefers to remain in bed. These symptoms, too, may of course have some origin other than osteoporosis, and it is clear that any attempt to appraise osteoporosis therapy solely on the basis of the patient's own assessment is most hazardous. The patients selected for this study, however, presented more severe symptoms, which were assumed to be due to the osteoporosis. Between 1967 and 1970 treatment was given to 17 patients with severe osteoporosis, and at the same time checks of the skeletal density were carried out. The age and sex distributions are presented in Table 1.

Figure 2. Patient using stairs with the infusion apparatus carried in a special device affixed to the back.

Diagnostic methods

A regular clinical examination, including a case history, was carried out, special attention being devoted to diseases that might affect the skeleton. No bone biopsy specimens were taken. Radiographs of the thoracic and lumbar spine in all cases indicated severe osteoporosis, usually with compression of the vertebrae (Figure 1).

Laboratory determinations of calcium, phosphorus, alkaline phosphatase and creatinine in the blood were made before and after the treatment, and, so far as calcium and phosphorus are concerned, also during the treatment. The erythrocyte sedimentation rate and the haemoglobin were determined on admission. The urinary sediment was examined before and after the treatment.

No systematic radiographic check was made after the treatment. The patients were regularly followed clinically for at least 2 years.

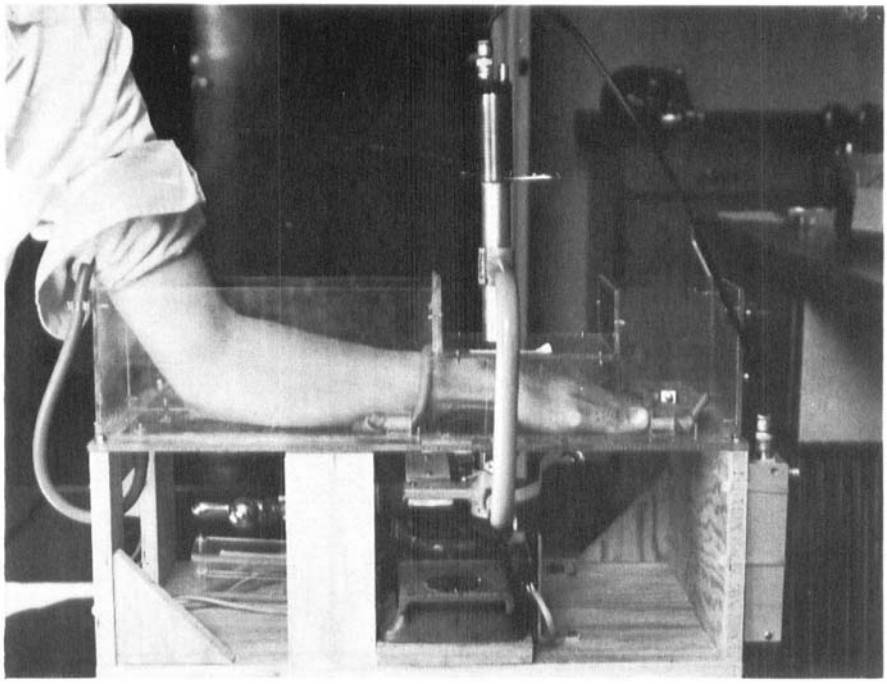

Figure 3. Apparatus for measuring the bone density in the ulna.

Methods of treatment

The calcium was administered by intravenous drop infusion and as calcium glyconate (Sandoz) dissolved in a 5.5 per cent glucose solution or, in cases of diabetes, in isotonic saline. The infusion solution contained 900 mg of calcium ions in 500 ml of prepared solution and was obtained by mixing 450 ml of the basic solution with 50 ml of a 20 per cent calcium glyconate solution. Because toxic or allergic reactions are sometimes obtained when commercial preparations of calcium glyconate are used, it is recommended that the original Sandoz preparation is used, especially when large doses are given.

The infusion rate was varied according to the individual tolerance, but usually 500 ml was given over 4 hours. Depending on the tolerance, between 400 and 1500 ml was given daily—usually 1000 ml. The treatment normally covered a period of 3–4 weeks. Over the full period of treatment each patient received an average of 27,000 mg of calcium ions (range 9000—62,100 mg). Since the infusion treatment usually took the greater part of a day and it was not considered advisable to keep the patients in bed throughout the period, a special support for the infusion apparatus was designed which enabled the patients to move around during the day, while the infusion was running (Figure 2). For exercise they were recommended to use stairs and the cycle ergometer, and, where possible, to participate in light gymnastic exercises.

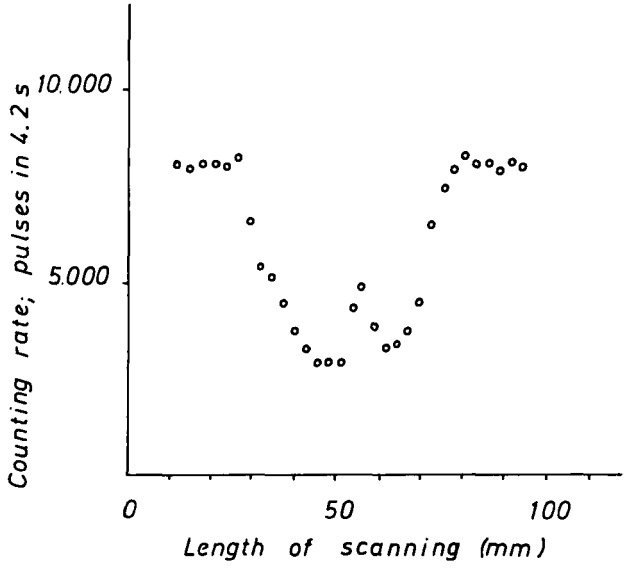

Figure 4. Measurement curve obtained in scanning over the ulna. Four such measurements are made at each examination. The mean of the 3 lowest values from each curve was used.

Criteria for improvement

The subjective improvement at the end of the treatment period was assessed in the usual way, by discussion with the patient, avoiding any leading questions and disregarding occasional polite phrases from the patient. The improvement was graded as slight, significant or pronounced.

An objective appraisal of the improvement was made by continuous determination of the bone density, usually three times a week. In the first 10 cases the density was measured at points on both femoral condyles, in the last 7 cases by scanning at a distal site on one (and the same) ulna. The density of the femoral condyles was measured by means of gamma radiation from ^{241}Am and a scintillation detector with a measuring time of one minute. The radiation dose with these measurements was of the magnitude of 20 mR/hour. One problem here was to ensure exact reproducibility of site and level. This was facilitated by tatooing marks on the skin and providing a special device for immobilizing the knee and lower leg. On each occasion an average of 3 measurements on each knee was made. The scatter with this method was of the order of 10 per cent, and it was therefore difficult to record any improvement in the individual case as the expected percentage increase in calcium level was at the same or a lower level. For this reason subsequent measurements were made on the ulna. For this purpose a scanning apparatus was constructed. Here the radiation source was ^{125}I and a scintillation detector was also used here. The distal part of the ulna was scanned twice at two levels about 5 cm apart (Figure 3). The arm was immersed in water. For each level of measurement a mean of the 3 values having the maximum

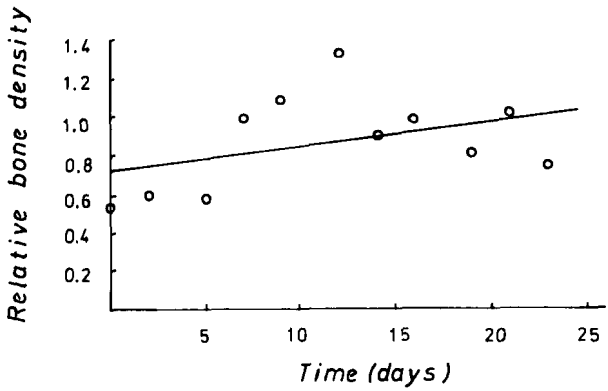

Figure 5. Patients for whom the individual measurement values of the relative bone density and the computed regression line have been drawn in.

absorption was used, and as the scanning was performed twice at each of 2 levels a mean of 12 individual measurement values was obtained for each subject at each examination (Figure 4). With this method the scatter was about 5 per cent. The relative calcium content was expressed in relation to measurement in water alone. For the knee a variable water phantom with the same thickness at the actual femoral condyle was used.

Statistical methods

For each subject a series of measurement values for the relative calcium content was obtained which covered a period from before the treatment up until treatment was completed. The mean number of individual values was 6 for the knee joint and 12 for the ulna. On the basis of these mean values a regression line was calculated for each subject. The percentage change in the relative calcium content according to the regression line was then computed (Figure 5).

The mean percentage change during the treatment for all 17 subjects, the standard error of the mean, the value of t and the individual correlation coefficient of the regression lines were calculated by the usual statistical methods (Snedecor 1968).

RESULTS

As seen in Table 2 all 17 patients considered that there had been an improvement. Some of the patients described the improvement as fantastic; prior to the treatment they had been more or less constantly confined to bed with back pain for up to 6 months.

The percentage change in the relative calcium content and other individual data are presented in Table 3. In 15 subjects it was positive, ranging from 0.8 to 45 per cent, and in 2 subjects it was negative, with

Table 2. Subjective improvement after the calcium therapy.

	Subjective improvement		
	Slight	Significant	Pronounced
Men	1	–	1
Women	3	2	10
Total	4	2	11

Table 3. Changes in bone density after treatment.

Case no.	Sex	Age	Duration of treatment (days)	Increase in density (per cent)*	Subjective improvement	Dose of Ca^{++} (mg)	Measuring site
1	F	72	25	+ 14.6	+++	31,500	Femur
2	F	56	31	+ 3.9	+++	27,000	Femur
3	M	48	16	+ 13.9	+	25,200	Femur
4	F	68	14	+ 45.4	+++	18,000	Femur
5	F	75	16	+ 5.7	+++	18,900	Femur
6	F	62	27	+ 45.0	+++	25,200	Femur
7	M	61	14	— 2.9	+++	9,900	Femur
8	F	63	27	+ 1.3	+++	28,000	Femur
9	F	71	7	+ 31.2	+	9,000	Femur
10	F	57	23	+ 22.1	+++	23,400	Femur
11	F	72	25	+ 2.3	+++	62,100	Ulna
12	F	72	18	+ 2.6	+++	39,600	Ulna
13	F	62	25	+ 1.8	+	44,100	Ulna
14	F	67	18	+ 10.8	+++	34,200	Ulna
15	F	63	25	— 2.5	++	24,300	Ulna
16	F	71	7	+ 1.6	+	7,200	Ulna
17	F	61	25	+ 0.8	++	36,000	Ulna
Mean		65	20	+ 11.6		27,270	

* These values were obtained from regression lines for each patient and do not indicate whether there was a significant rise (fall) in the individual case.

low values of 2.5 and 2.9 per cent. The mean percentage change was 11.6 ± 3.8 and significant ($0.01 > P > 0.001$).

On the radiographs of the back after the treatment no definite changes in the degree of osteoporosis could be detected. The calcium and phosphorus levels in the serum both before and after the treatment were within the normal ranges, and there was no evident tendency for a rise or fall during the treatment.

Table 4. Side effects.

The serum calcium level increased from 10—15—18 mg/100 ml (i.e. 5—7.5—9 mEq/l)
Hot in face and body
Fatigue, muscle weakness
Headache, malaise
Vomiting, increase in blood pressure
Disturbed balance
Impaired hearing and vision

Complications

No onset of renal calculus or haematuria was discovered during the treatment or the follow-up period. In some patients small increases in creatinine concentration in plasma were recorded after the treatment, but they were within the normal range. During the infusion, subjective symptoms of intolerance were reported (Table 4). In connection with such symptoms the blood calcium was often determined, and rises from 10 to 14–15 and in one case 18 mg/100 ml were noted (9 mEq/l). It is of great importance to instruct the ward staff concerning various subjective symptoms of intolerance; the first step in such cases is to reduce the infusion rate, or even to interrupt the infusion until the next day. In one subject where, by error, the infusion was continued in spite of severe symptoms of intolerance (malaise, headache and vomiting) the patient had marked disturbance of balance, with difficulty in walking unsupported and marked impairment of hearing and vision; the serum calcium was then 18 mg/100 ml. After discontinuing the treatment and giving cortisone intravenously all the symptoms regressed in 24 hours. There was no longer any trace of the hearing or visual defect, and no explanation for them could be offered. If the infusion rate is low and a lookout is kept for side effects the treatment can usually be carried out without appreciable discomfort. The maximum rate could generally be found by trial: the tolerated daily dose of calcium for the individual subject ranged from 800 and 2,700 mg. Since significant changes in plasma calcium level occur, the treatment should be used only with great caution, if at all, in patients on digitalis therapy or with suspected or manifest arrhythmia.

After-treatment and late results

After the treatment the patients were given calcium citrate and vitamins C and D by mouth (calcium 1050 mg, vitamin C 150 mg and

vitamin D 3000 I U a day), usually as Casal D C ®, 10 tablets a day. An orthopaedic corsette was likewise usually worn and the patients were recommended to take ample physical exercise in the form of walks and light gymnastics. At the follow-up checks at intervals 3–6 months the subjective improvements were usually maintained or increased, and there was no evidence subsequently of renal calculus or any other kidney disease.

DISCUSSION

The improvements in the relative calcium content obtained in the individual cases with the computed regression lines for all the individual determinations showed in no case a significant rise. The method error and the scatter of the individual values were too large for this. The change was significant only when the results for all 17 subjects were combined.

In an earlier study of clinical osteoporosis, where bone biopsy specimens were taken from crista iliaca, Lindahl (1960) found that not one of 70 consecutive cases of osteoporosis revealed any sign of osteomalacia. More recent investigations by Buring (1970) have shown that there is possibly reason to shift the accepted borderline between the current concepts of "osteoporosis" and "osteomalacia". Using a special technique not requiring demineralization of the bone specimens, it was found that osteoid tissue was considerably more common than was previously thought, probably because in conventional techniques the specimens are demineralized, with the result that the milder grades of osteomalacia can no longer be detected. It is possible that some of the present patients had "osteomalacia" that could not be diagnosed by conventional techniques. There were, however, no signs of osteomalacia that could be detected clinically or by laboratory tests, or that were suspected from the history.

As it is inconceivable that so much new bone tissue could have been formed in the course of one month, the increase in density must be ascribed in the first place to an increase in the degree of mineralization and to calcification of any osteoid tissue.

In 1969 Barrier reported a good subjective effect of calcium infusions in osteoporosis and also various laboratory data pointing to an improvement. No density measurements were performed. He saw no evidence of renal damage.

In a group of osteoporosis patients given calcium infusions Jensen & Toft (1971) reported a case of "acute hypercalcaemic syndrome" in a patient with a plasma calcium level of 20.2 mg/100 ml. The patient, who was obviously in a poor general state, recovered in 4 days when cortisone and phosphate infusions were supplied. The authors recommend that when such treatment is given it should be checked that the glomerular filtration rate is normal and that the plasma calcium level has returned to normal after the previous infusion.

The calcium treatment should, of course, be given only with the greatest caution, if at all, to patients with impaired renal function; but experience shows that subjective symptoms are the best warning signal of a too intensive treatment and hypercalcaemia, and care should be taken to instruct the staff and the patient about the symptoms of intolerance.

In view of the antagonism between calcium and potassium, care is probably also indicated in the case of patients where there is reason to suspect disturbance of the potassium metabolism—for instance, after treatment with hypertensive agents.

SUMMARY

Large amounts of calcium (on average 27,000 mg given over 4 weeks) were administered as an intravenous infusion to patients with severe osteoporosis. The patients reported a marked improvement, and a mean rise in the bone density of 11.6 per cent was recorded in measurements on the femoral condyles or the distal part of the ulna by means of gamma radiation from ^{125}I and a scintillation detector. This objective improvement is statistically significant ($0.01 > P > 0.001$).

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