

Does Long-term Treatment with D-penicillamine Alter Calcium and Phosphorus Metabolism in Patients with Systemic Sclerosis?

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Hagdrup H, Serup J, Tvedegaard E. Does long-term treatment with D-penicillamine alter calcium and phosphorus metabolism in patients with systemic sclerosis? *Acta Derm Venereol* (Stockh) 1983; 63:447-449.

Only animal experiments have been published regarding the possible effect of penicillamine treatment on mineral balance. We examined 35 patients with a diagnosis of systemic sclerosis treated with penicillamine, in comparison with 10 patients with systemic sclerosis treated with other collagen inhibitors (glutamine, hydralazine, phenytoin, chlorpromazine). The following laboratory tests were performed in all patients: the serum concentrations of calcium, ionized calcium, phosphorus and the parathyroid hormone. The 24-hour urinary excretions of calcium and phosphorus were determined. The bone mineral content of the distal radius was determined by photon-absorptiometry; radiological examination of the hands was performed to show aberrant calcifications. No differences were found between the two groups. A low urinary excretion of calcium and phosphorus was found in the entire material. The bone mineral content was low in both groups. A high frequency of aberrant calcifications was not correlated to treatment with penicillamine. (Received December 13, 1982.)

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Few reports have been published about the possible effect of penicillamine treatment on the mineral balance.

In guinea pigs, penicillamine treatment was found to increase the urinary excretion of both calcium and phosphorus. The intestinal absorption of calcium was increased, whereas the absorption of phosphorus was reduced, and the calcium balance was negative in half of the animals (1).

Litin et al. have reported a slightly increased urinary excretion of calcium during penicillamine treatment in 3 patients with Wilson's disease, but in a later study they found no effect (2, 3).

The purpose of the present study was to determine the bone mineral content and evaluate the calcium and phosphorus metabolism in a group of patients after years of treatment with penicillamine.

MATERIAL AND METHOD

Patients with a diagnosis of systemic sclerosis (fulfilling the requirements of The American Rheumatism Association) treated at the Department of Dermatology, Rigshospital, participated in the study. Patients with known endocrine diseases and patients receiving hormonal therapy, including corticosteroids, were excluded from the study.

Thirty-five patients (28 women, 7 men) received treatment with penicillamine in a standard dose of 750 mg daily. The mean duration of treatment was 4.1 years (range 0-13 years). The treatment was routinely supplemented with oral glutamine, 600 mg daily.

Ten patients (9 women, 1 man) were not treated with penicillamine, but received other medications (glutamine, hydralazine, phenytoin, chlorpromazine). These patients were used as a control group.

The mean age of the 45 patients was 54.9 years (range 20-69 years), and the mean duration of systemic sclerosis was 10.0 years (range 3-30 years). The penicillamine-treated and the control groups were comparable with respect to age, duration of the disease, severity of the disease (radiological changes of the oesophagus and chest, Raynaud phenomena, soft tissue calcifications, teleangiectasia,

and serum creatinine). Interviews disclosed no differences in the diets of patients receiving penicillamine treatment vis-à-vis the 10 controls.

Analyses of blood and urine were performed by routine laboratory techniques and included the serum concentration of total calcium, ionized calcium, and of phosphate. The 24-hour urinary excretion rates of calcium and phosphorus were determined. The parathyroid hormone in serum was measured at Medicinsk Laboratorium A/S, Copenhagen, by a radioimmunoassay.

In 37 patients the bone mineral content (BMC) of the distal part of the radius was measured by Americium²⁴¹ photon absorptiometry *ad modum* Madsen et al. (4). The value was expressed as a percentage of the mean value of a group of healthy controls matched for age and sex.

Radiological examination of both hands was performed to diagnose calcifications of the soft tissues.

Mean values were compared by Student's *t*-test. Frequencies were compared assuming the Poisson distribution. Correlations were calculated by the least squares method. Probabilities less than 0.05 were considered statistically significant.

RESULTS

In Table I the results of analyses of blood and urine are shown. Statistically, there were no differences among the groups, and no differences as compared with the normal ranges. There was a tendency for urinary excretion of calcium and phosphorus to be low within the normal range.

BMC was reduced ($p < 0.05$) in the whole group of patients suffering from systemic sclerosis. There was no difference between the groups with vs. without penicillamine treatment. BMC did not change during treatment with penicillamine (Fig. 1).

Radiological examination revealed soft tissue calcifications in 15 of 35 patients treated with penicillamine, and in 4 of 10 patients receiving other medication. This difference was not statistically significant.

DISCUSSION

This study shows that routine laboratory parameters of calcium and phosphate metabolism and the parathyroid hormone are not significantly altered during long-term treatment with penicillamine.

In contrast to the study in guinea pigs, we found no increase in the renal excretion of calcium and phosphate, and there was no decalcification of the radius attributable to the treatment.

The high frequency of soft tissue calcifications in this material could not be correlated to penicillamine treatment, and, consequently, penicillamine seems not to precipitate calcification in the tissues.

Table I. Calcium and phosphate analyses of serum (S) and urine (U) of patients suffering from systemic sclerosis, related to treatment with penicillamine

		Penicillamine treatment, <i>n</i> = 35 Mean (range)	Other treatment, <i>n</i> = 10 Mean (range)	Normal range
S-Calcium 'total'	mmol/l	2.41 (2.27– 2.67)	2.40 (2.30– 2.49)	2.20– 2.60
S-Calcium ion	mmol/l	1.19 (1.01– 1.29)	1.21 (1.14– 1.28)	1.15– 1.35
S-Phosphate	mmol/l	1.19 (0.82– 1.45)	1.20 (0.63– 1.37)	0.80– 1.50
S-Parathyroid hormone	µg/l	0.44 (0.28– 0.60)	0.50 (0.33– 0.65)	0.22– 0.50
U-Calcium	mmol/24 h	3.20 (0.70– 7.10)	2.90 (0.90– 5.30)	2.00– 8.00
U-Phosphate	mmol/24 h	14.50 (4.00–35.00)	14.90 (2.30–24.00)	10.00–45.00

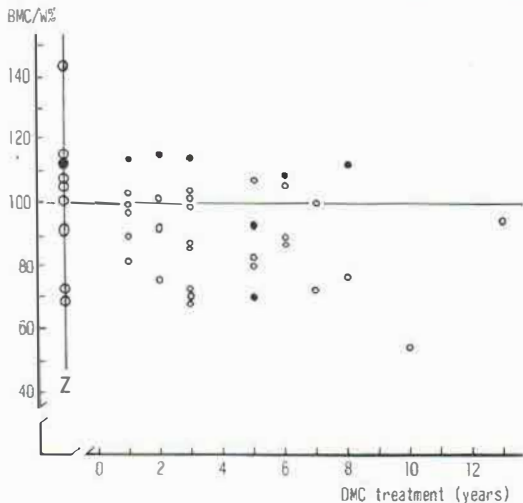


Fig. 1. Bone mineral content (BMC/W, g/cm^2) of the distal part of the radius related to duration of treatment with penicillamine, expressed as a percentage of the mean value of healthy controls matched for sex and age. Patients receiving other treatments than penicillamine are shown on the Z-line. \circ , women; \bullet , men.

Our results indicate that long-term treatment with penicillamine can be given safely with no precautions regarding calcium metabolism.

REFERENCES

1. Djafar, M. I., Camberos, H. R. & Davis, G. K.: Effect of D-penicillamine treatment on mineral balance in quinea pigs. *J Nutr* 97: 117, 1969.
2. Litin, R. B., Goldstein, N. P., Randall, R. V. & Diessner, G. R.: Hypercalciuria in Wilson's disease with data on the effect of D-penicillamine on the urinary excretion of calcium and copper. *J Lab Clin Med* 52: 923, 1958.
3. Litin, R. B., Goldstein, N. P., Randall, R. V., Powers, M. H. & Diessner, G. R.: Effect of D-penicillamine on the urinary excretion of copper and calcium in hepato-lenticular degeneration (Wilson's disease). *Neurology* 10: 123, 1969.
4. Madsen, S.: Calcium and phosphate metabolism in chronic renal failure, with particular reference to the effect of 1 α -hydroxyvitamin D_3 . *Acta Med Scand* (Suppl. 638), 1980.