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Longitudinal Changes in Forearm Bone Mineral Content in Primary Hyperparathyroidism

J. WARNER, P. CLIFTON-BLIGH, S. POSEN, A. McELDUFF, L. DELBRIDGE, and T. REEVE

ABSTRACT

Forearm bone mineral content was measured in 28 patients with primary hyperparathyroidism before and 1 year after successful parathyroidectomy. The forearm bone mineral content rose from a mean value of 1.068 to 1.092 g/cm ($P < 0.05$, paired *t*-test). Those patients with the lower initial values had the largest rise. In an additional study, the forearm bone mineral content was measured in 10 women over the age of 40 years (mean age 58.6 ± 7.9SD years) with hyperparathyroidism before and for 2 years after successful parathyroidectomy and compared with the forearm bone mineral content measured over 2 years in 12 women (mean age 56.3 ± 5.5SD years) with continuing hyperparathyroidism and with the forearm bone mineral content of 12 eucalcemic control women (mean age 58.8 ± 8.2SD years), also measured over 2 years. The parathyroidectomized group gained bone, whereas the ongoing hyperparathyroid group and the eucalcemic control group lost bone. The difference between the parathyroidectomized group and the ongoing hyperparathyroid group was significant after 2 years ($P < 0.05$). The percentage loss of forearm bone mineral in the eucalcemic control subjects was not significantly different from the percentage loss of forearm bone mineral in the ongoing hyperparathyroid group, although the initial mean bone mineral content in the eucalcemic group was significantly higher than in the ongoing hyperparathyroid group, suggesting that a possible determinant of bone mineral loss in women in this age group is the initial bone mineral content.

INTRODUCTION

PRIMARY HYPERPARATHYROIDISM has been associated with excessive loss of bone mineral, which is believed to result from hyperstimulation of osteoclastic bone resorption by excessive amounts of circulating parathyroid hormone.[1–5] Cross-sectional studies of patients with primary hyperparathyroidism have shown diminished bone mineral content measured by photon absorptiometry[6–8] and by quantitative computed tomography.[9,10] In severe disease, conventional radiography may reveal subperiosteal erosions, lytic lesions, and diffuse osteopenia.[1,5,10–12] An increased prevalence of vertebral crush fractures has also been reported,[12,13] although there is some uncertainty about the suitability of the control groups in these studies. Parathyroidectomy in patients without overt complications of the disease is controversial.[14–22] Increasing availability of bone mineral densitometry has allowed postoperative changes in specific bones to be monitored. Some investigators found no change after parathyroidectomy; others reported significant increases.[6,12,23–26] In many of these studies, however, other factors that may influence bone mass were not rigorously sought and simultaneous studies of appropriate control populations were not undertaken. When an increase in the bone mineral density after parathyroidectomy has been observed, it has been short term, with no further increase seen by the end of the second postoperative year.[23,24,30] On the other hand, untreated hyperparathyroidism has been shown in some studies to be associated with a decline in bone mineral content.[6,23]

In the present study, the bone mineral content of the distal forearm was measured in patients before and after parathyroidectomy and compared with changes in the

Departments of Endocrinology and Surgery, Royal North Shore Hospital, St. Leonards, New South Wales, Australia.

forearm bone mineral content measured in patients with continuing hyperparathyroidism and in normal control subjects.

PATIENTS AND METHODS

Between 1983 and 1986, 244 patients with primary hyperparathyroidism were evaluated. The diagnosis was based on the finding of an elevated serum calcium concentration, an elevated serum parathyroid hormone, and an absence of other causes of hypercalcemia. A number of patients with primary hyperparathyroidism did not undergo parathyroidectomy because they lacked symptoms and signs associated with hyperparathyroidism and were regularly followed. Of the 244 patients, 136 had parathyroidectomy and 92 did not; 16 patients had advanced renal failure and were excluded from the present analysis. The indications for parathyroidectomy generally were a serum calcium of more than 3.00 mmol/liter, a history of peptic ulceration, and the occurrence of renal calculi, pancreatitis, renal impairment, or muscle weakness. Patients who had measurements of forearm bone mineral content at the time of diagnosis and for up to 2 years subsequently were considered further and were compared with eucalcemic control patients who were studied over the same interval of time. Patients or control subjects who were taking glucocorticoids, thyroxine, phenytoin, thiazide diuretics, estrogens, progestins, anabolic steroids, calcitonin, vitamin D, or excess alcohol were excluded from analysis. Patients or control subjects who had celiac disease, osteomalacia, chronic hepatitis, rheumatoid arthritis, or diabetes mellitus were excluded. Those with a serum creatinine >0.20 mmol/liter were excluded. One patient in the parathyroidectomized group had a gastrectomy 18 years before parathyroidectomy. She was not taking vitamin D. The forearm bone mineral content was measured in the dominant arm in each patient or control subject with a Novo osteodensitometer. The values are given as g/cm. Measurements of the bone mineral content were commenced at a point where the distal radius and ulna were 8 mm apart, and six sweeps were made proximally. The precision of measurement was 1%.

After the exclusions mentioned, the remaining patients were divided into four study groups. In group A, 28 patients with primary hyperparathyroidism (21 women and 7 men, aged between 20 and 77 years) underwent parathyroidectomy and were rendered eucalcemic. Measurements of bone mineral content were made either before or within a few days of surgery and at least once again during 12 months after surgery. Groups B, C, and D, described here, represent three age-matched groups of females over the age of 40.

Group B, 10 women over the age of 40 with primary hyperparathyroidism, were treated successfully with parathyroidectomy and rendered eucalcemic. The mean age was 58.6 ± 7.9 years, mean ± standard deviation (SD). Initial measurements of bone mineral content were made either before surgery or within a few days of surgery. The 10 patients in this group are also included in group A.

Group C, 12 women over the age of 40 with hypercalcemia due to hyperparathyroidism, were not subjected to parathyroidectomy (9) or remained hypercalcemic after unsuccessful surgery (3). The mean age was 56.3 ± 5.5 (SD).

Control group D consisted of 12 eucalcemic women over the age of 40 years (mean age 58.8 ● 8.2 SD years). In groups B, C, and D estimates of forearm bone mineral content were made at 0, 12, and 24 months. Serum calcium and creatinine concentrations were measured by standard autoanalyzer methods. Serum parathyroid hormone was measured by a method previously described.[27] The normal range for this assay is 0–0.4 ng/ml. The polyclonal antiparathyroid hormone antibody used in the radioimmunoassay "sees" the whole 1–84 human parathyroid hormone molecule but not the C-terminal fragments. The assay is a one-site radioimmunoassay.

RESULTS

In group A, 28 patients aged between 20 and 77 years were studied over a 12 month period following successful parathyroidectomy. The mean forearm bone mineral content at time zero was 1.068 g/cm ± 0.412 (SD) and rose over a 12 month period by 0.024 g/cm, or 2.25% ($P <$ 0.05 paired t-test). The 28 patients were ranked from 1 to 28 in terms of initial forearm bone mineral content. The 14 patients with higher initial bone mineral content (above 0.927 g/cm), whose mean age was 41.9 ± 16.7 years (SD), showed a mean change of +0.004 g/cm over the 12 month period from 1.354 to 1.358 g/cm (SD), whereas the 14 patients with the lower initial bone mineral content (below or equal to 0.927 g/cm), whose mean age was 59.6 ± 9.7

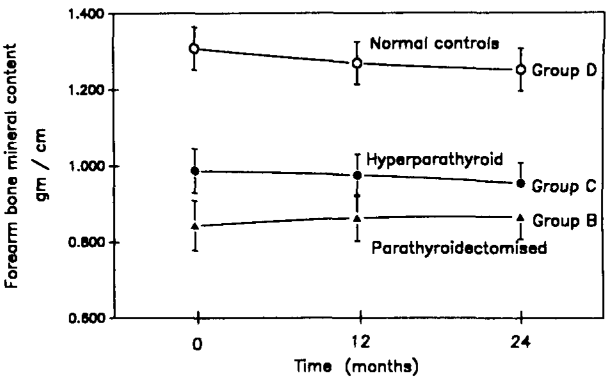

FIG. 1. Mean changes in the forearm bone mineral content over a 2 year period in women over the age of 40 who underwent successful parathyroidectomy (group B), who remained hyperparathyroid (group C), compared with normal control subjects (group D). Each data point shows the mean ± SEM (standard error of the mean). The significance of the changes in each group and comparisons between groups are given in the text.

(SD) years, showed a mean change of 0.045 g/cm from 0.781 to 0.826 g/cm ($P < 0.025$). The difference between the mean ages of the two groups was significant ($P < 0.005$).

In group B, 10 women over the age of 40 years underwent successful parathyroidectomy for hyperparathyroidism and were followed for 2 years. The mean serum calcium before parathyroidectomy was 3.02 ± 0.26 (SD) mmol/liter (range 2.65–3.40). The mean PTH before surgery was 1.51 ± 0.60 (SD) ng/ml. The mean forearm bone mineral content at the time of surgery was 0.843 ± 0.208 (SD) g/cm and rose by a mean of 0.021 g/cm, or 2.49%, over 2 years to 0.864 ± 0.183 (SD) g/cm. The greatest part of the rise, 2.25%, occurred in the first 12 months, and 0.24% in the second 12 months. The rise in the bone mineral content over the 2 year period was not significant.

In group C, 12 women over the age of 40 years were studied with ongoing hyperparathyroidism. The mean serum calcium was 2.83 ± 0.14 (SD) mmol/liter (range 2.61–3.04). The mean serum PTH was 0.75 ± 0.28 (SD) ng/ml. The mean forearm bone mineral content at the time of initial assessment was 0.987 ± 0.201 (SD) g/cm and over a 2 year period fell by a mean of 0.035 g/cm, or 3.55%, to 0.952 ± 0.190 (SD) g/cm. The fall in the bone mineral content over the 2 year period was not significant. In the 9 patients who had not had a neck operation the initial mean bone mineral content was 0.967 g/cm and the mean fall in bone mineral content was 0.040 g/cm. In the 3 patients who had an unsuccessful neck exploration the initial mean bone mineral content was 1.049 g/cm, falling by a mean of 0.026 g/cm.

In group D, 12 normal women over the age of 40 years were studied. They were not on any medications known to influence bone mass and had no intercurrent previous illness known to influence bone mass. The mean forearm bone mineral content at the time of initial assessment was 1.308 ± 0.193 (SD) g/cm and over a 2 year period fell by a mean of 0.057 g/cm, or 4.36%, to 1.251 ± 0.193 (SD) g/cm. The fall was significant ($P < 0.001$, paired t-test). The mean fall in forearm bone mineral content of the eucalcemic control subjects in group D was not significantly different from the fall in the ongoing hyperparathyroid group C. The mean fall in the forearm bone mineral content of the control subjects was significantly different compared to the mean rise in the forearm bone mineral content in the parathyroidectomized patients in group B ($P < 0.005$). Also the mean fall in the forearm bone mineral content for the ongoing hyperparathyroid group was significantly different from the mean rise in the forearm bone mineral content of the parathyroidectomized group ($P < 0.05$). The changes in the bone mineral content in groups B, C, and D are shown in Figure 1.

The percentage change over a 2 year period between the control group and the untreated hyperparathyroid group was not significantly different. If the percentage losses of bone in the control group and the untreated hyperparathyroid group were combined and then compared with the percentage gain in bone in the parathyroidectomized group B, there was a significant difference ($P < 0.005$), suggesting that parathyroidectomy and restoration of eucalcemia did in some way prevent bone loss during the 2 years of observation.

The initial bone mineral content in the ongoing hyperparathyroidism group and in the parathyroidectomized group before surgery did not correlate with the serum calcium or with the serum PTH. The change in bone mineral content in the ongoing hyperparathyroid group over a 2 year period did not correlate with the serum PTH.

The forearm bone mineral content of the control group at time zero, 1.308 g/cm, was significantly different from both the forearm bone mineral content at time zero in the group with ongoing hyperparathyroidism, 0.987 g/cm ($P < 0.001$), and from the forearm bone mineral content at time zero in the parathyroidectomized group B, 0.843 g/cm ($P < 0.001$). The forearm bone mineral content at time zero in the group with ongoing hyperparathyroidism (group C) was not significantly different from the forearm bone mineral content at time zero in the group who had successful parathyroidectomy (group B).

DISCUSSION

In a group of 28 patients with primary hyperparathyroidism, both men and women of diverse age, who were studied for 1 year after successful parathyroidectomy, the forearm bone mineral content rose significantly by 2.25%. Furthermore, those patients who had the lower initial bone mineral content and who were also older showed the largest increase in the 12 month period. This is similar to the data of Mautalen et al.,[24] except that age was not taken into account in this latter study. Mautalen et al.[24] also showed a high negative correlation between the initial forearm bone mineral content and the subsequent rise in bone mass. A separate aspect of the present study was the evaluation of three groups of women of similar mean age (over the age of 40 years) for a 2 year period. Many of this group of 34 women had a past hysterectomy or could not remember exactly when menopause occurred, but because the mean ages of the three groups was not significantly different, it was assumed that any influence of menopause on bone mineral loss in the three groups would be comparable. In addition, any patient who had an intercurrent disease or was receiving ongoing medication that might influence bone mineral content was excluded from the study. An important finding was that, whereas the normal eucalcemic control subjects and ongoing hyperparathyroid patients lost bone, those having a successful parathyroidectomy did not. The difference between the eucalcemic control subjects and the parathyroidectomized group was significant. In the female parathyroidectomized group B there was a small nonsignificant rise in the forearm bone mineral content over 2 years, and it seems unlikely that the forearm bone mineral content would ultimately be restored to control values. Martin et al.[30] also found that the increment in forearm bone mineral content that occurred after parathyroidectomy was less with each succeeding year. However, Alhava et al.[26] found that forearm bone mineral content increased toward normal control values for 4-5 years after parathyroidectomy, but thereafter increased rates of loss were again observed.

In the present study, patients with ongoing hyperparathyroidism lost bone, compared to the initial bone mineral content, at the same percentage rate as normal control subjects, notwithstanding that their baseline bone mineral content was significantly lower than the forearm bone mineral content of control subjects. The question arises as to why patients with hyperparathyroidism have lower forearm bone mineral content compared to age- and sex-matched control subjects. It has usually been assumed that low bone mineral content is due to excess resorption of bone by osteoclasts under the influence of increased circulating parathyroid hormone over a prolonged period. If this process is proportional to the initial bone mineral content, then bone loss follows an exponential function. If patients with hyperparathyroidism originally had normal bone mass before the onset of hyperparathyroidism, then taking into consideration the rate at which bone loss was observed in this study, hyperparathyroidism must have been present for many years before diagnosis, or, during an earlier time before the commencement of the present observation, there may have been an accelerated loss of bone mineral. The concept that excess parathyroid hormone is an important factor responsible for bone loss is supported by the finding that bone mineral content increased after the serum parathyroid hormone was rendered normal by parathyroidectomy (group A). An alternative possibility is that intrinsically low bone mineral content may predispose an individual to an increase in parathyroid function and subsequent hypercalcemia, rather than increased parathyroid activity causing a low bone mineral content. If the former is true, then the rate of loss of bone mineral would not correlate with the serum PTH, and this was the case in the present study. Also, in another study,[8] the serum PTH did not correlate with the forearm bone mineral content although relationships between serum PTH and a single measurement of the bone mineral content do not take into account the influence of the time that the excess parathyroid hormone has been operating at the bone cell level. In the present study, the group with ongoing hyperparathyroidism, with a mean serum calcium of 2.82 mm/liter, had a percentage loss of bone mineral over a 2 year period that was similar to the percentage loss of bone mineral in normal control subjects, and this finding is similar to that observed by Rao et al.[28] in patients with comparable degrees of hyperparathyroidism. Also in the latter group, an increased risk of minimal trauma fracture was not observed,[29] in contrast to the findings of other groups.[12,23] We do not have any data on the incidence of fracture in our group of patients.

The decision to carry out a neck exploration for hyperparathyroidism is based upon an assumed benefit from parathyroidectomy. If patients with mild hyperparathyroidism do not have an increased risk of minimal trauma fracture, then restoration of eucalcemia by surgery does not confer benefit in skeletal terms. In the present study, however, those patients with the lowest forearm bone mineral content, 0.927 g/cm or lower, had the largest rise in bone mineral content after successful parathyroidectomy (5.76% in 1 year), and this may allow some reduction in the risk of minimal trauma fracture, although this is not proven.

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Address reprint requests to:
Dr. P. Clifton-Bligh
Department of Endocrinology
Royal North Shore Hospital
St. Leonards, NSW 2065, Australia