Prediction of Bone Loss in Patients with Primary Hyperparathyroidism Using Quantitative Bone SPECT

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Bone loss is a major complication of primary hyperparathyroidism (PHPT), and it has significant implications in the treatment of this disease. Bone turnover was measured in patients with PHPT, using quantitative bone SPECT (QBS), to determine if the rate of bone loss could be predicted before a significant decrease in bone mass occurs. **Methods:** Forty-six patients were included in the study. QBS and bone mineral density (BMD) of the lumbar spine (LS) and femoral neck (FN) were done at baseline. The percent deviation of QBS in patients with PHPT from the values in normal matched controls was calculated. BMD was measured again after a mean of 17.5 mo in 38 patients, and in 29 patients a repeat BMD study was done after a mean of 41.4 mo. The change in BMD in patients with high and normal QBS values was compared using the nonparametric Mann-Whitney test. Regression analysis tested the correlation between baseline QBS values and BMD changes over time. **Results:** For the FN, there was a statistically significant difference in the BMD change between patients with high and normal QBS values for short-term follow-up ($-2.82\% \pm 4.80\%$ versus $1.45\% \pm 4.67\%$, $p < 0.05$) and for long-term follow-up ($-3.53\% \pm 5.34\%$ versus $0.92\% \pm 2.40$, $p < 0.02$). There was a negative correlation in the FN, $r = -0.48$ between QBS values and the percentage of change in BMD. There was no significant difference between the percentage of change in BMD in the LS in patients with high and normal QBS values for either short- or long-term follow-up. **Conclusion:** The results of this study show that QBS can predict bone loss in the FN in patients with PHPT. QBS can thus indicate the need for surgery at an early stage of the disease to prevent bone loss.

Key Words: hyperparathyroidism; quantitative SPECT; bone loss

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Bone loss is a major complication of primary hyperparathyroidism (PHPT), and the extent of bone loss is an important factor in indicating the need for surgery (*1–3*). Although an increase in bone mineral density (BMD) has been reported during the first years after successful parathyroidectomy (*3,4*), bone repair may be incomplete and bone mass often remains lower than normal. It also has been suggested that newly formed bone may be qualitatively inferior (*5*). The significance of bone loss in asymptomatic PHPT is not clear. The data on the amount and rate of loss of BMD and the incidence of fractures in these patients are controversial (*3*). However, the presence of osteopenia in patients with asymptomatic PHPT generally is considered to be an indication for surgery (*1*). BMD measures the effect of previously elevated parathyroid hormone (PTH) serum levels on the bone and determines the amount of bone mass present at the time of the study (*5*), but it does not indicate the rate at which bone is lost. There are large variations in BMD in the normal population (*6*). Low bone mass does not necessarily mean rapid bone loss. High bone mass does not rule out the onset of recent rapid bone loss due to PHPT. BMD may be normal in patients who lose bone quickly but who started with high BMD values and vice versa. Currently, no clinically accepted technique can determine prospectively which patients with PHPT will lose bone and would benefit from surgery. Prediction of bone loss could lead to prevention of osteoporosis and its associated morbidity. In this study, we examined whether quantitative bone SPECT (QBS) (*7–10*) can determine which patients, with symptomatic and asymptomatic PHPT, are at high risk of bone loss. These patients should receive more aggressive treatment, and surgery should be performed to prevent osteoporosis.

MATERIALS AND METHODS

Between 1991 and 1994, 65 consecutive patients with PHPT were enrolled in a longitudinal study designed to test the ability of QBS to predict bone loss. Diagnosis of PHPT was based on elevated levels of serum calcium, increased urinary calcium excretion, decreased levels of serum phosphorous and increased levels of PTH. Nineteen patients were not available for follow-up (13 patients underwent surgery soon after their initial evaluation, and 6 did not comply with the study protocol). We report on the 46 patients [40 women (6 premenopausal), 6 men; age range 34–76 yr; mean age 57.6 yr] who had follow-up measurement of BMD. One of these patients underwent bilateral hip replacement and had evaluation of the lumbar spine (LS) only. Twenty-six patients had ultrasound or CT evidence of a parathyroid adenoma. Twelve patients had an adenoma demonstrated by scintigraphy. Eight patients did not have imaging evidence of an adenoma. At presentation, the mean serum levels of calcium were 11.7 ± 0.6 mg/dl, of alkaline phosphatase 121.3 ± 55.5 SI units and of PTH 118.1 ± 59.5 pg/ml. Causes of hypercalcemia other than PHPT were excluded. No patient had a history of renal, liver or other chronic illness. No patient had a history of steroid treatment. Two patients were on thyroid hormone replacement therapy. Twenty-two patients were asymptomatic. Twenty-four patients had bone pain, muscular weakness and nephrolithiasis due to PHPT. In 14 of the symptomatic patients, surgery was performed at a later stage. Surgery was not performed in 7 symptomatic patients who refused it, in 2 symptomatic patients who had a deterioration of their general status due to causes not related to PHPT and in 1 patient with bone pain who was at high surgical risk. During the study period, 15 of the 46 patients received oral phosphates, 1 patient received vitamin D and 1 patient received calcitonin. Their

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treatment was started before they entered the study, and it was not changed during the study period.

Patients had both QBS and BMD examinations on entering the study, and they had later repeat BMD measurements. Mean values of BMD in the LS at presentation were 1.00 ± 0.22 g/cm^2 (29 patients had normal values, and 17 patients had decreased bone density). Mean values of BMD in the femoral neck (FN) at presentation were 0.81 ± 0.15 g/cm^2 (33 patients had normal values, and 12 patients had decreased bone density). Since some of these patients did not comply completely with the follow-up protocol, a different number of patients was available for analysis at each point in the follow-up. A period of 24 mo was chosen arbitrarily as the threshold between short- and long-term follow-up. Short-term follow-up was performed in 38 patients after a mean 17.5 mo (range 11–24 mo). Long-term evaluation was done in 29 patients after a mean 41.4 mo (range 28–60 mo). Twenty-one patients had both short- and long-term follow-up measurements. Twenty-five patients had only two BMD (baseline and follow-up) measurements. Seventeen of those patients were reevaluated only during a period shorter than 24 mo (4 underwent subsequent surgery, 8 were not available for further follow-up and 5 patients who were enrolled only during the later part of the study did not have enough time for follow-up). Eight patients were re-evaluated only after more than 24 mo.

The technique of QBS has been described previously (*8–10*). SPECT of the LS and FN was performed 3 hr after intravenous injection of 20 mCi ^{99m}Tc-methylene diphosphonate (MDP) (Soreq Nuclear Laboratory, Yavne, Israel). QBS values of the second, third and fourth lumbar vertebrae and the FN were measured. These were the same regions used for BMD measurements. A large-field-of-view (Apex 415) or very-large-field-of-view (SP-6) digital gamma camera with a rotating gantry (Elscint, Haifa, Israel) was used. A complete rotation of 360°, 120 projections, 3° apart over 20 min was performed, with acquisition of about 6×10^6 counts. Raw data were reconstructed using filtered backprojection with a Hanning filter and a cutoff point of 0.5 cycle/cm using a SP-1 computer (Elscint). After SPECT reconstruction, each image was sectioned at 1-pixel (0.68 cm) intervals in the transaxial, coronal and sagittal planes using a 64 × 64 matrix. For concentration measurements, calculations were performed on the reconstructed data using the threshold method (*7*). A threshold of 43%, which in previous studies was found to give the smallest error in a wide range of phantom studies, was used to measure the concentration of ^{99m}Tc-MDP in the bone. This threshold is suitable for the range of ^{99m}Tc-MDP concentrations encountered in the bone (*7*). Counts/pixel were converted to concentration units (μCi/cc), and the percentage of injected dose ^{99m}Tc-MDP per cc (%/ID/cc) of bone tissue was calculated using the identity line of counts/pixel and μCi/cc (*7,8*). The percentage injected dose of ^{99m}Tc-MDP per cc $\times 10^{-3}$ of bone tissue is defined as the QBS value. Using this method, SPECT-measured concentrations in phantoms showed a good correlation (r = 0.98) to known concentrations. When an in vivo SPECT-measured concentration of ^{99m}Tc-MDP in patients was compared to the gold standard of concentration in the same bones obtained during surgery, measured in vitro, the correlation (r = 0.96) was also good (*8*). Phantom studies have shown a coefficient of variation for replicate studies of less than 2%. There was no significant difference between two studies done several months apart in the same group of patients, which indicates a precise technique (*8*). The percentage of deviation in QBS value in each patient from the mean value for an age- and sex-matched normal population of 158 healthy individuals in our database was calculated on the basis of the equation:

$$[QBS_p - QBS_n/QBS_n \times 100],$$

where QBS_p = the patient's QBS value and QBS_n = the normal mean QBS value in a healthy population matched for sex and age. QBS was considered abnormally elevated when it was higher than the mean plus one s.d. of the normal value matched for age and sex.

Vertebral and FN BMD were measured using the dual energy x-ray absorptiometry method using a commercial instrument (Lunar, Wisconsin, MD). The results of measurements of the second, third and fourth lumbar vertebrae and the FN were expressed in grams divided by the projected area of these skeletal areas in square centimeters. The commercial computer program provided by the manufacturer was used. The data of our normal controls matched these data. Phantom studies showed that the coefficient of variation for same day replicate measurements was less than 1%. The long-term variability in the stability of the instrument was less than 1%. The percentage change in bone density in each patient was calculated according to the equation:

$$[BMD_2 - BMD_1/BMD_1 \times 100],$$

where BMD_1 = BMD at baseline and BMD_2 = BMD at the time of the follow-up.

Results of QBS at baseline and BMD at baseline and at follow-up were expressed as mean ± s.d. The percentage of change in BMD patients with high QBS values (percent positive deviation of QBS at baseline compared to the mean normal value plus one s.d.) was compared to the percentage of change in BMD in patients with normal QBS for both the LS and FN. Statistical analysis of the difference in percentage of change BMD in patients with high and normal QBS was done using the nonparametric Mann-Whitney test. Regression analysis was used to assess the correlation between the QBS values and the percentage of change in BMD.

RESULTS

Of the 46 patients included in the study, 21 patients, 11 symptomatic and 10 asymptomatic, had high QBS values in the LS when they entered the study, with a mean percent positive deviation of 169.8% ± 26.4%. Twenty-five patients, 13 symptomatic and 12 asymptomatic, had QBS values in the LS within the normal range, with a mean percent deviation of 101.8% ± 18.2%. Twenty-two patients, 11 symptomatic and 11 asymptomatic, had high QBS values in the FN, with a mean percent positive deviation of 187.2% ± 40.4%. Twenty-three patients, 12 symptomatic and 11 asymptomatic, had QBS values in the FN within the normal range with a mean percent deviation of 106.8% ± 18.9%.

The mean percentage of change in BMD for short-term follow-up in 16 patients with high QBS in the LS was −2.25% ± 4.38% and in 22 patients with normal QBS, 0.32% ± 4.72%, p not significant (<0.2). For long-term follow-up, the mean percentage of change in BMD in the LS in 16 patients with high QBS was −3.75% ± 4.70% versus −0.38% ± 7.93% in 13 patients with normal QBS values, p not significant (<0.2). There was a significant difference between the mean percentage of change in BMD in the FN for short-term follow-up in 17 patients with high QBS and in 20 patients with normal QBS values, −2.82% ± 4.80% versus 1.45% ± 4.67%, $p < 0.05$. There was also a significant difference in the mean percentage of change in BMD in the FN for long-term follow-up between 15 patients with high QBS and 13 patients with normal QBS values, −3.53% ± 5.34% versus 0.92% ± 2.40%, $p < 0.02$ (Table 1). The individual points of change in BMD for short- and long-term follow-up in patients with high and normal QBS values in the FN are shown in Figure 1.

No correlation was found between QBS values and the percentage of change in BMD in the LS for short-term follow-

TABLE 1
Quantitative Bone SPECT (QBS) Values and Changes in Bone Mineral Density (BMD) in Lumbar Spine and Femoral Neck with Primary Hyperparathyroidism

	QBS	Change in BMD (%) short-term follow-up	Significance (p)	Change in BMD (%) long-term follow-up	Significance (p)
Lumbar spine	169.8 ± 26.6	−2.25 ± 4.38		−3.75 ± 4.70	
High QBS	(n = 21)	(n = 16)	$p < 0.2$	(n = 16)	$p < 0.2$
Normal QBS	101.8 ± 18.2	0.32 ± 4.72		−0.38 ± 7.93	
	(n = 26)	(n = 22)		(n = 13)	
Femoral neck	187.2 ± 40.4	−2.82 ± 4.80		−3.53 ± 5.34	
High QBS	(n = 22)	(n = 17)	$p < 0.05$	(n = 15)	$p < 0.02$
Normal QBS	106.8 ± 18.9	−1.45 ± 4.67		0.92 ± 2.40	
	(n = 23)	(n = 20)		(n = 13)	

up. A weak negative correlation was found in the LS for long-term follow-up, r = −0.33. There was a good negative correlation (r = −0.48) between QBS values in the FN and the percentage change in BMD for both the short- and the long-term follow-up groups.

DISCUSSION

Bone loss is a major complication of PHPT. High PTH levels have a catabolic effect, particularly on cortical bone, with relative sparing of cancellous bone. PTH causes increased osteoclastic activity preferentially on cortical bone compared to trabecular bone (*4,5,11*). Iliac crest bone biopsies, correlated with BMD measurements in asymptomatic patients with PHPT, showed changes in only the cortical bone (*12,13*). Bone loss is an important factor in determining the need for excision of a parathyroid adenoma. Although on follow-up after surgery there is improvement in bone mass, bone repair may be incomplete. After removal of a parathyroid adenoma, BMD increases but may remain below normal values, even when PHPT has been cured (*5,14*). Therefore, surgery should be performed early before significant bone loss has occurred. With the widespread use of biochemistry screening tests, there is an increase in the incidence of hypercalcemia and, subsequently, in the diagnosis of asymptomatic PHPT in patients who have no complaints and no clinical findings (*12*). The data on the presence and severity of bone disease in patients with asymptomatic PHPT are controversial (*1*). Some authors report bone involvement in only 20% of patients (*15*), whereas others find it in most patients (*12*). When the BMD is normal in patients with asymptomatic PHPT, routine surgery is not considered necessary (*13,16*).

BMD at each point in life is determined by the peak bone mass and the rate of bone loss (*5*). BMD has to be remeasured at 1- to 2-yr intervals to assess whether a substantial amount of bone has been lost during this period. The decision to recommend surgery in patients with PHPT based on only abnormally low values of bone density is controversial. There has been no way to determine prospectively which patients will lose bone quickly and, therefore, require surgical removal of an abnormal parathyroid. Delaying surgery in patients with PHPT who lose bone will result in osteoporosis. Bone complications of PHPT are reversible when treated early, before a significant amount of bone is lost. When treated too late, bone disease may progress in spite of successful surgery.

QBS is a noninvasive, accurate and precise in vivo test for the measurement of bone turnover (*7,8*). In a previous study, it was found that approximately 50% of patients with PHPT have high

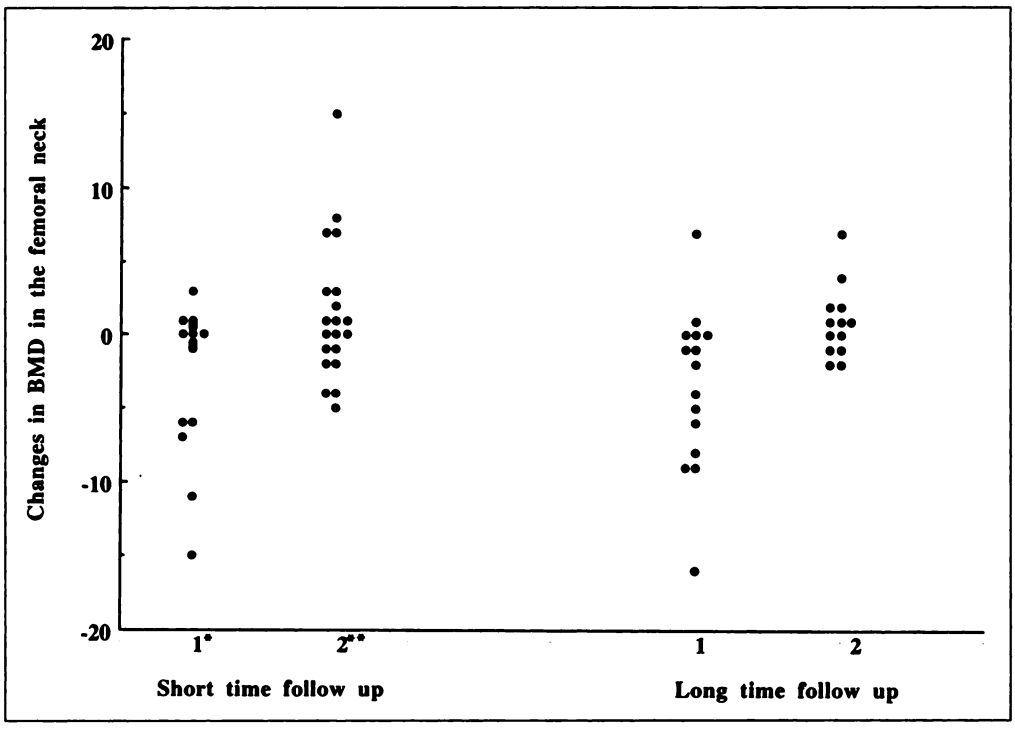

FIGURE 1. Changes in bone mineral density for short- and long-term follow-up in patients with high and normal quantitative bone SPECT (QBS) values in femoral neck. 1* = patients with high QBS values; 2** = patients with normal QBS values.

QBS values that returned to normal 3 mo after successful surgery (*9*). The most significant abnormalities in that study were seen in the FN and shaft, which consist predominantly of cortical bone (*9*). Prediction of bone loss was possible when using the QBS technique in patients with renal osteodystrophy and secondary hyperparathyroidism (*10*). High QBS values, expressing high bone turnover, predicted rapid bone loss, with a sensitivity of 78% for the LS and 100% for the FN and a specificity of 71% and 78%, respectively. The correlation between QBS and the percentage of change in BMD was better in patients with chronic renal disease in the FN than in the LS, similar to the results in this study. PTH affects cancellous bone less than cortical bone, and this explains the different results for the lumbar vertebrae, although there was a similar trend of change in spinal BMD.

CONCLUSION

Present results indicate that patients with PHPT who have elevated QBS values in the FN show significant bone loss compared with patients with normal bone turnover. The results are similar in patients with symptomatic PHPT and those with asymptomatic disease. QBS, therefore, has the potential for identifying the subgroup of PHPT patients who will lose bone. Measurement of QBS in patients with PHPT assesses bone turnover, and it can predict early rapid cortical bone loss. High QBS values may indicate the need for surgery to prevent irreversible bone loss.

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Technetium-99m-Sestamibi Parathyroid Scintigraphy: Effect of P-Glycoprotein, Histology and Tumor Size on Detectability

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The purpose of this study was to evaluate the effect of P-glycoprotein (P-gp) levels, predominant histology and tumor size on the detectability of parathyroid adenomas with ^{99m}Tc-sestamibi scans. Although previous studies have shown that positivity correlates with tumor size, false-negative studies have been reported with large tumors and true-positives reported with very small tumors. Recent investigations have reported rapid washout of sestamibi in malignant tumors because of high levels of P-gp, similar to that seen with multidrug chemotherapy resistance. Therefore, we postulated that this mechanism might account for false-negative studies in parathyroid tumors. Preliminary reports have suggested that the predominant histological subtype influences positivity on ^{99m}Tc-sestamibi parathyroid scans. **Methods:** We studied 25 patients with surgically confirmed parathyroid adenomas with ^{99m}Tc-sestamibi parathyroid scans. The results of the imaging study were correlated with tissue P-gp levels, predominant histological subtype and size of the surgically removed glands. **Results:** There were 21 true-positive and 4 false-negative results. The size of the adenomas ranged from 0.12 to 8.64 ml. We found no correlation between the results of the dual-phase ^{99m}Tc-sestamibi study and either the predominant cell type or the level of P-gp. Positivity did correlate with the size of the adenoma ($\rho = 0.73$, $p < 0.0001$). We cannot exclude the possibility that P-gp and cell type may still play a role in individual cases, but we suspect that other yet to be determined factors may influence ^{99m}Tc-sestamibi detectability in addition to tumor size.

Key Words: parathyroid; p-glycoprotein; histology; volume

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Dual-phase ^{99m}Tc-sestamibi parathyroid scans are commonly performed in our institution for the preoperative localization of parathyroid adenomas. The overall accuracy has been high, but false-negative studies occasionally occur (*1*). Investigators (*1–3*) have reported a correlation between tumor size and detectability of parathyroid adenomas by sestamibi parathyroid scintigraphy. However, some very small tumors have been

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