Quantitative Bone Scintigraphy in Patients with Hyperparathyroidism

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Laboratory tests, including the determination of parathormone in serum, and x-ray examinations are often of limited value in diagnosing hyperparathyroidism (HPT). In this study, bone scintigraphy was carried out in 15 patients with proven HPT (primary and secondary in patients with chronic renal disease) and 25 normal subjects, to evaluate quantitatively increased bone metabolism. The count density ratios bone to soft tissue (D/S-index) were calculated. In normal, this D/S index averaged 3.66 ± 0.94 and was significantly ($p < 0.001$) different to that of HPT-patients averaging 6.37 ± 1.64. The quantitative evaluation shows a sensitivity of 73%, a specificity of 100% and an accuracy of 90% for detecting HPT (based on the sample values). Discriminant analysis can be applied to calculate the probability of the presence of HPT (primary and secondary) as a function of the measured D/S index.

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Hyperparathyroidism (HPT), primary and secondary in patients with chronic renal disease, is characterized by excessive production of parathyroid hormone (*1,2*). The diagnosis is based on changes of several parameters of blood and urine (sometimes borderline serum calcium elevation and low phosphorus, calciuria and phosphaturia), elevation of parathyroid hormone in serum (*3,4*), radiographic abnormalities of the skeleton such as bone cysts, subperiosteal resorption of the phalanges, "salt and pepper" skull (*5,6*), and on kidney diseases (nephrolithiasis, nephrocalcinosis). Increased parathormone activity causes decalcification with osteolyses in bone (*7,8*). Therefore scintigraphy is also used to evaluate metabolic bone disease in patients with HPT (*9,10,11*). The literature reports typical scintigraphic signs of increased accumulation in the long bones, distinguished uptake in skull and mandible, chain-like appearance of the bone cartilage border of the rib cage and other pathologic structures (*12,13*).

However, these signs can be found only in advanced stages of the disease. This study tries to detect and quantify the increased bone metabolism associated with increased parathyroid hormone secretion in an earlier stage.

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PATIENTS AND METHOD

Fifteen patients with histologically proven HPT (eight with primary and seven with secondary HPT in chronic renal disease) were studied. The control group of 25 subjects consisted of patients with primary neoplasm of various organs without clinical suspicion of skeletal metastases. In this group the result of the routine bone scanning was negative. All studies were performed with a gamma camera and microcomputer system. Approximately 15 to 25 mCi (11.1 MBq per kg body weight) technetium-99m methylene diphosphonate ([^{99m}Tc]MDP) were administered intravenously. A static image of both femurs (400,000 counts per image) was performed 6 hr after injection (3 hr after conventional whole-body bone scanning) in order to minimize the effect of different plasma clearance.

Individual regions of interest (ROIs) of 100 pixels each were delineated as follows: (a) in the central parts of the right and left diaphyses of both femurs, and (b) in the medial parts of the soft tissue areas of both thighs. The diaphysis/soft tissue-index (D/S) was calculated from the count densities in both of these regions (Fig. 1). The average value of these two indices was taken for analysis. The discriminant analysis was carried out by calculating the probability of the presence of HPT as a function of the D/S index. Because there was no statistically significant difference between primary and secondary HPT with respect to the D/S index we were able to collect all HPT patients in one group.

RESULTS

The mean value of the D/S index in patients with HPT was 6.37 (s.d. = 1.64 and 3.66 (s.d. = 0.94) in the

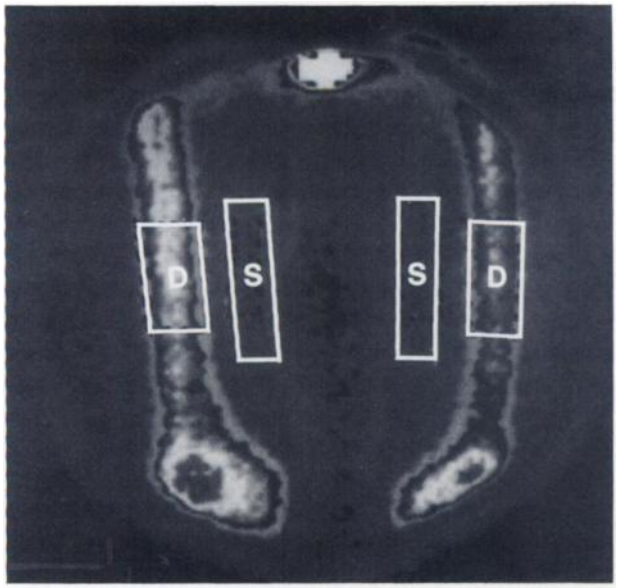

FIGURE 1
Individual ROIs—diaphysis (D) and soft tissue (S) areas of both thighs.

normal group, respectively. The difference between these values was significant ($p < 0.001$). The mean value plus 2 s.d.s calculated for healthy subjects yielded 5.54, which was accepted as the upper limit of the normal range. Values below this limit were observed in all subjects of the normal group (specificity = 100%). In 11 of the 15 HPT patients the values of the D/S index were >5.54 (sensitivity = 73%). Two patients with primary and two patients with secondary HPT were within the high normal range. All subjects suffering from HPT or not, were detected with an accuracy of 90%. Between the D/S index in patients with primary and secondary HPT there was no statistical difference: the mean value of the D/S index in primary HPT was 6.0 (s.d. = 0.84); in secondary HPT 6.37 (s.d. = 1.83).

STATISTICS

The calculation of the above mentioned values for sensitivity (73%) and specificity (100%) is based on the two collectives of examined patients. The measured data permit the use of normal distributions of the D/S index for further calculations, tested with the Shapiro-Wilk statistic (*14*). Thus far, assuming normal (Gaussian) distribution for either the healthy (Fig. 2 N) and for the HPT group (Fig. 2 HPT), either, we may expect a specificity of 98% and a sensitivity of 69% in the stochastic mean, if the criterion for decision is like the one used in the previous paragraph (D/S >5.54 means diagnosis HPT). Based on these data, a discriminant analysis (*15*) was carried out. The appropriate normalized HPT distribution demonstrates the probability of the presence of HPT (primary and secondary) as a function of D/S index (Fig. 3).

DISCUSSION

An increased focal or generalized skeletal activity as a result of increased bone uptake of [^{99m}Tc]phosphate,

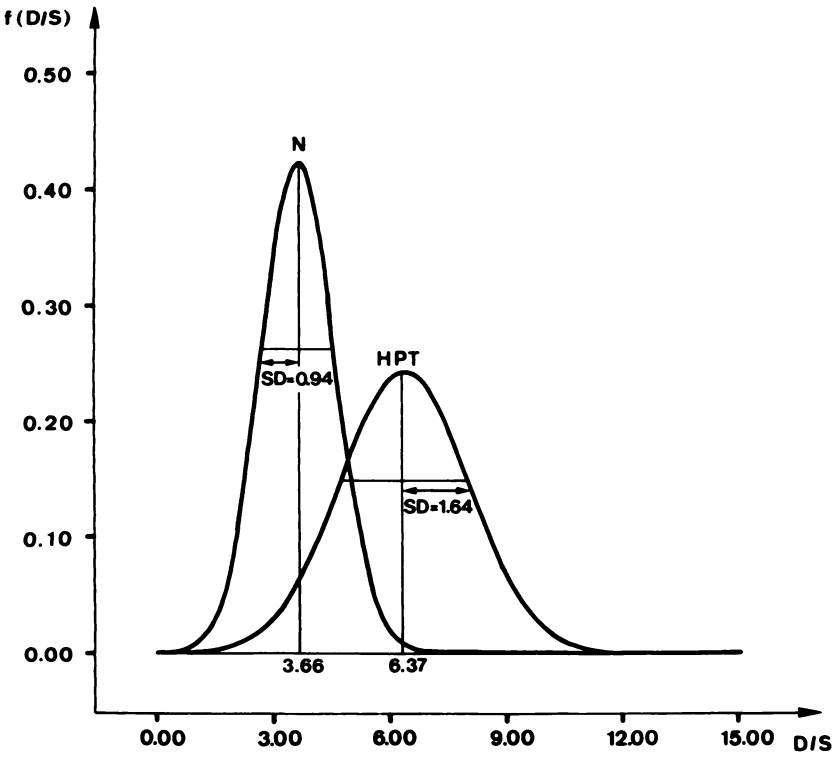

FIGURE 2
Distribution (f) of the diaphysis/soft-tissue index (D/S) based on the investigated normal subjects (N) and the patients with primary and secondary HPT.

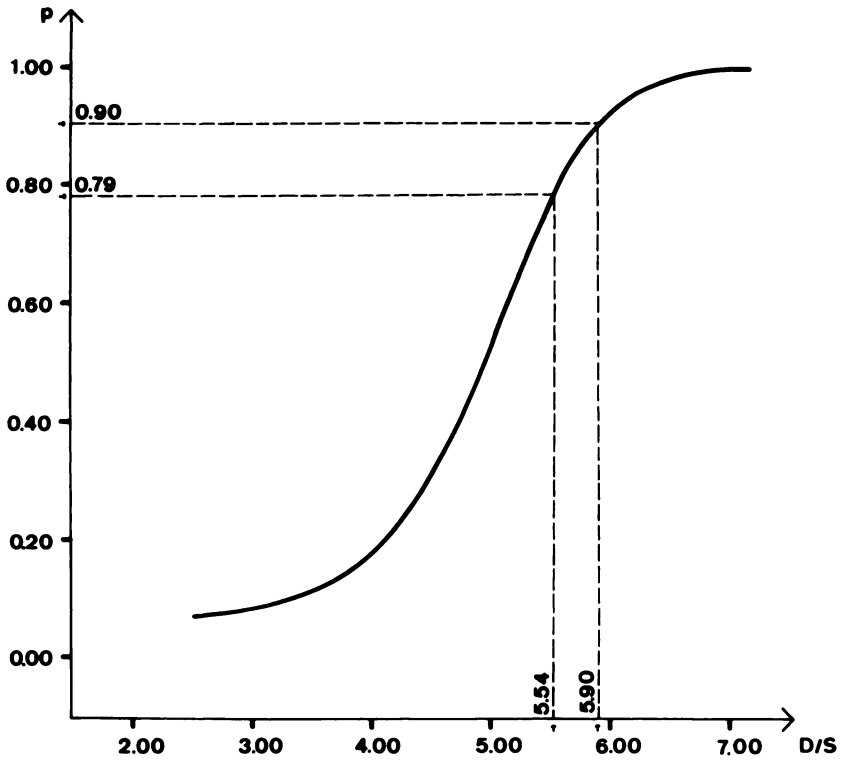

FIGURE 3
Probability (p) of the presence of primary and secondary HPT as a function of the diaphysis/soft-tissue index (D/S). For example, the probability for HPT is 0.90 for a D/S = 5.90, and 0.79 for D/S = 5.54.

is observed on bone scans in metabolic bone diseases including HPT. Abnormal bone collagen metabolism is suspected as a cause of this phenomenon (*11,16*). Qualitative and quantitative radionuclide methods are applied to recognize abnormal bone metabolism in HPT. Qualitative diagnosis of metabolic abnormalities depends upon typical scintigraphic signs such as an increased activity in the axial skeleton, long bones and in periarticular areas, a prominent calvarium and mandible, beading of the costo-chondral junctions, "tie-like" sternum, and faint or absent kidney images (*12,13*). However, these signs are mainly observed in advanced stages of the disease. The subjective evaluation of these signs also limits the value of the qualitative method.

Quantitation of skeletal radiotracer uptake is performed using bone to soft-tissue ratios, whole-body retention of [^{99m}Tc]phosphates (*19,20*) and [^{99m}Tc] phosphate clearance (*21,22*). The real value of these radionuclide methods is still a matter of discussion.

Measurement of bone-to-soft-tissue ratios has been proposed by Wiegmann (*16,23*), Holmes (*24*), Lien (*25*), Rosenthall (*9*), Fogelman (*19*), Brecht-Krauss (*18*). In the opinion of Fogelman and Wiegmann (*23,26*) the bone-to-soft-tissue index is of limited value in detecting HPT.

Our results demonstrate, indeed, that the sensitivity of the bone-to-soft-tissue index in recognizing HPT is relatively low (73%): in 11 of 15 HPT-patients the D/S index was greater than 5.54. However, the specificity is very high (100%): the D/S index was elevated in none of the normals.

This finding cannot be depreciated by the well-known fact that increased bone uptake can also be observed in a number of other metabolic bone diseases such as Paget's disease, osteomalacia, thyroitoxicosis, and acromegaly (*19,26,27*). Most of these diseases show characteristic symptoms and can be differentiated easily from HPT.

The usefulness of the bone-to-soft-tissue index in diagnosing HPT is demonstrated in Figure 3, which shows the probability of HPT (primary and secondary) dependent on the value of the D/S index: For example, a D/S index of 5.54 (= mean value of control group ± 2 s.d.) gives a probability of 79% for HPT. This on first sight may not be in accordance with the properties of Gaussian distributions, but is due to the overlapping of the values of the two collectives (Fig. 2). A higher D/S index, e.g., 5.9, means that the probability of HPT is in excess of 90%. In these cases the diagnosis, in patients in which HPT is suspected, can be based on the above mentioned radionuclide technique. We conclude that the bone-to-soft-tissue index may be helpful in the recognition of metabolic bone disease in patients with suspected HPT.

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