# Quantitative Bone Scintigraphy Using SPECT

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A quantitative single photon emission computed tomography (SPECT) technique for measuring radiopharmaceutical uptake in humans has been applied to bone scintigraphy. The method was validated by comparing SPECT measured percent of injected [$^{99m}$Tc]MDP in 16 normal skulls with well counter measurements of samples of the same bones obtained at surgery. A very good correlation (r = 0.96) was found. A very good interobserver correlation (r = 0.99) and agreement were also obtained when using quantitative bone scintigraphy (QBS). Control SPECT studies of uptake in the right and left iliac bones and the right and left sacroiliac regions in each patient showed no significant differences between the contralateral sides. Studies done in seven subjects at 2 and 4 hr after the same injection and in nine subjects 4 to 8 mo later in the same subjects showed a very good agreement and no significant differences between the two measurements were found. QBS is suggested as an accurate and reproducible index for assessment of the mass of remodeling bone. Preliminary results showed differences in QBS of normal subjects at different ages. A group of 68 young patients aged 18–26 yr showed a significant higher QBS ($p < 0.001$) when compared to an older group of 62 patients aged 50–85 yr. There was, however, a wide range of uptake values for the same bone in the same group, suggesting that the method should best be used for following individual patients over time.

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Bone scintigraphy is an extremely sensitive method for detection of focal bone disease. It has become the clinical standard for detection of metastatic disease, early osteomyelitis, and occult fracture. It is, however, seldom used for the evaluation of diseases which involve the entire skeleton. This has been the result of the lack of good methods for quantitation of bone scintigraphy. Presently bone scintigraphy is judged subjectively by a visual comparison of regions with increased uptake, which are considered abnormal, to the normal bone. The interpretation of bone scintigraphy is essentially binary—a lesion exists or does not exist. Diseases such as osteoporosis and other metabolic diseases, which cause diffuse changes in uptake throughout the entire skeleton cannot usually be detected.

The present study was initiated with the idea of quantitating the high sensitivity inherent in bone scintigraphy. The aim of the study was first to evaluate if quantitative single photon emission computed tomography (SPECT) (*1–4*) could be applied to bone scintigraphy. The technique was tested by the gold standard of in vivo/in vitro comparison. SPECT measured patient bone uptake was compared with in vitro measurements of samples of the same bone obtained at surgery. The reproducibility and repeatability of this technique in bone studies was examined.

The second aim was to measure normal QBS in patients in different age groups in order to detect differences between them and the range of differences within the same age group.

## MATERIAL AND METHODS

A SPECT technique for absolute quantitation of radiopharmaceutical uptake in patients in vivo has been previously described in detail (*1–4*). A SPECT camera (Apex 415-ECT, Elscint, Haifa, Israel) and a medium resolution, medium sensitivity low-energy collimator (APC-3-Elscint Haifa, Israel) were used. For quantitative bone scintigraphy a complete rotation of 360° of the camera detector, 120 projections, 3° apart and a study of 20 min were used. At 2 hr after the

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injection ~$6 \times 10^6$ counts were required for the whole study. The raw data were reconstructed by a filtered backprojection using a Hanning filter. The filter is described in the frequency domain as:

$$F(w) = 0.5w\,[1 + \cos(\Pi w/n)]$$

$\Pi = 3.14153$

where: $w$ = frequency

$n$ = Nyquist frequency

Data were stored on an Imagecenter (ImageCenter-Sudbury Systems, Sudbury, MA) optical disk. After reconstruction each image was sectioned at 1 pixel (0.68 cm) intervals along the transaxial, sagittal and coronal planes. A $64 \times 64$ byte matrix was used. Calculations were then performed directly on the reconstructed data (Fig. 1).

We have used the threshold method for measurement of volume and concentration. In a series of phantom studies which evaluated different thresholds it was found that a threshold of 43% gives the smallest error in a wide range of volumes and concentrations *(1,3)*. It is suitable for clinical measurement of various organs. The pixel containing the maximum number of counts within a region of interest in all the sections selected to define the bone was determined and the threshold value of 43 was calculated by the computer as a percentage of the counts within this pixel. Only those pixels containing activity greater than the threshold were used for calculating volumes and concentrations. A voxel was defined as pixel multiplied by the slice thickness. Counts per voxel were translated into absolute uptake using phantom data reported previously (*1,3*). Counts per voxel were converted to concentration units (μCi/cc) and subsequently to percent of injected

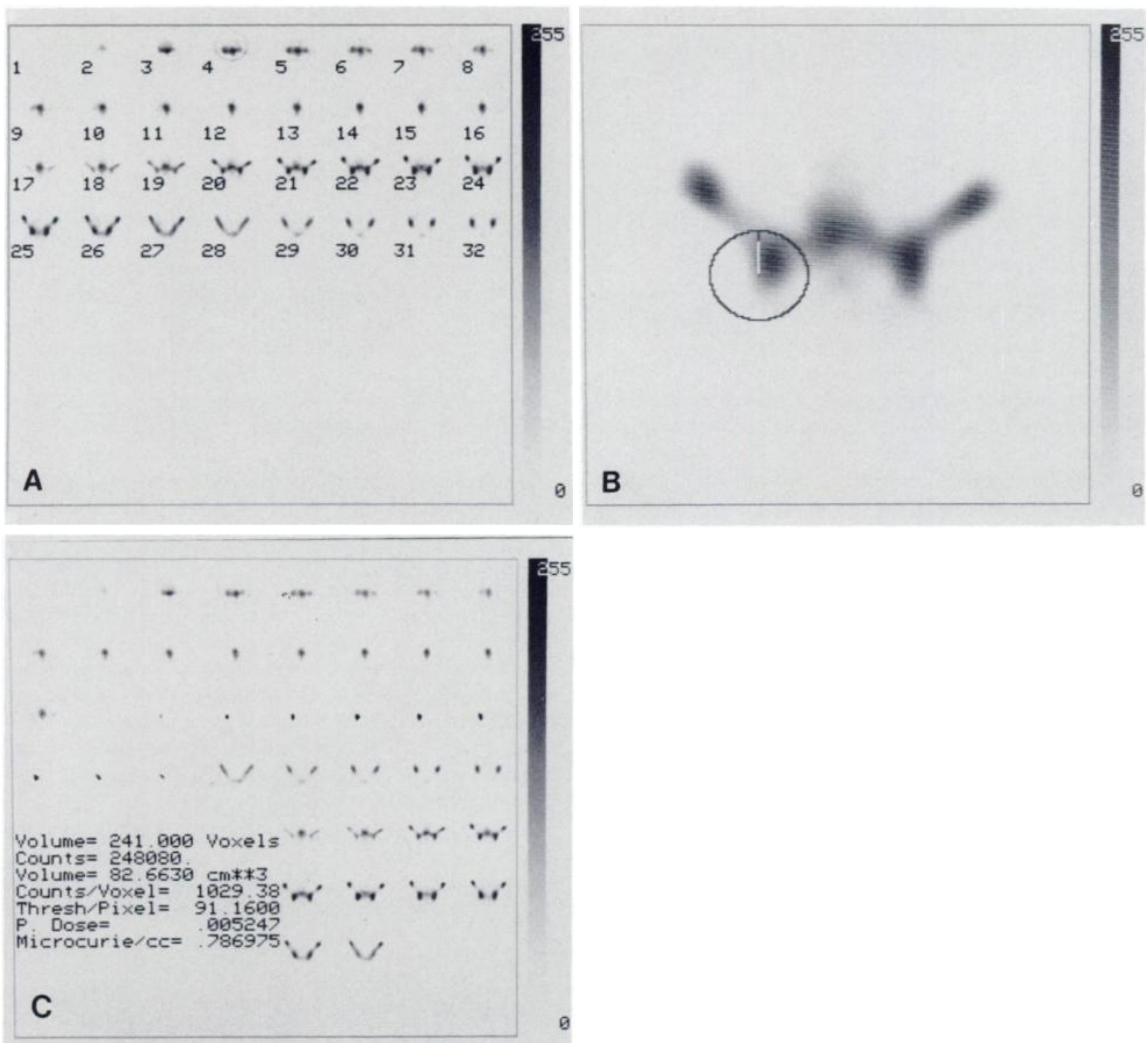


**FIGURE 1**
Measurement of QBS. A: Numbered (1–32) reconstructed SPECT images of the pelvic region. B: The slice selected (no. 21) for drawing a sacroiliac region of interest. Threshold calculations are automatically done by the computer for the preselected slices (18–27). C: Results of QBS calculations for right sacroiliac.

dose using the regression line of the comparison of phantoms with known concentrations to the SPECT measurements of counts per voxel (*1,3*). By using this regression line and the number of counts per voxel provided by the program in each QBS study the concentration can be calculated. The program asks for the amount of injected activity. The percent of injected dose for the selected region is calculated with a correction for radioactive decay. It should be realized that when other equipment or other reconstruction algorithms are used, the threshold value and SPECT values of phantom concentrations used for conversion of counts per voxel to μCi/cc should be first tested. A series of phantom measurements as previously described (*3*) should be performed. Also, the performance of the system should be routinely checked using the NEMA [National Electronical Measurement Association, 2101 L Street, NW, Washington DC 20037] guidelines and a series of phantoms of different volumes and concentrations. In the studies reported here the threshold was used for masking for volume calculations and the threshold value (43%) was subtracted from each of the voxels to correct for count density. This threshold was found empirically to give the best results over a large range of volumes and concentrations (*3*). A very good correlation (r = 0.99) was found between SPECT measured volume and actual phantom volumes in phantoms of 30 to 3,800 cc (*3*). A similar correlation (r = 0.98) was found in concentrations of 0.01 to 3.6 μCi/cc, which includes the range of concentrations of technetium-99m methylene diphosphonate ([$^{99m}$Tc]MDP) in bone (*3*). A close correlation was also found when in vivo SPECT measurements of concentrations of various Tc-labeled agents were compared to in vitro measurements of samples of brain tumors (r = 0.84) (*1*), lung tumors (r = 0.92) (*2*), and blood (r = 0.95) (*3*).

We wished to validate the method for bone measurements as well. Sixteen patients with neurosurgical diseases that did not involve the skull had an in vivo/in vitro comparison of [$^{99m}$Tc]MDP uptake in their skulls. Patients had quantitative SPECT of the entire vault of the skull at 2, 4, and 6 hr after the injection of 20 mCi of MDP. There were no significant differences between the 2, 4 and, 6 hr measurements. Craniotomy was performed 3 to 7 days after the SPECT study. Before surgery, 1 mCi of [$^{99m}$Tc]MDP was injected intravenously. Samples of ~1.2 g of bone were obtained at surgery 2 to 6 hr after injection. Only samples which contained whole bone (the two tables of the skull) were measured. The bone was cleaned from adherent extraosseous tissue using a scalpel and the radioactivity determined in a well counter without further manipulations. Corrections were made for radionuclide decay. The average of the percent of injected dose per gram for all samples of bone obtained at surgery was compared with the values obtained in the in vivo SPECT studies of the entire vault of the skull.

To establish normal values, QBS was performed in four groups of investigational subjects using 20 mCi of [$^{99m}$Tc]MDP injected i.v. in each patient. Twenty-six young females and 42 young males, age 18–26 yr (mean 19.8 for women and 19.4 for men) were compared with an older group of 37 females and 25 males, age 50 to 85 yr (mean 62 yr for women and 65.1 yr for men). All subjects had no evidence of bone disease and planar bone scintigraphy of the entire skeleton was normal. The iliac bones, sacroiliac regions, and lumbar vertebrae were studied by QBS.

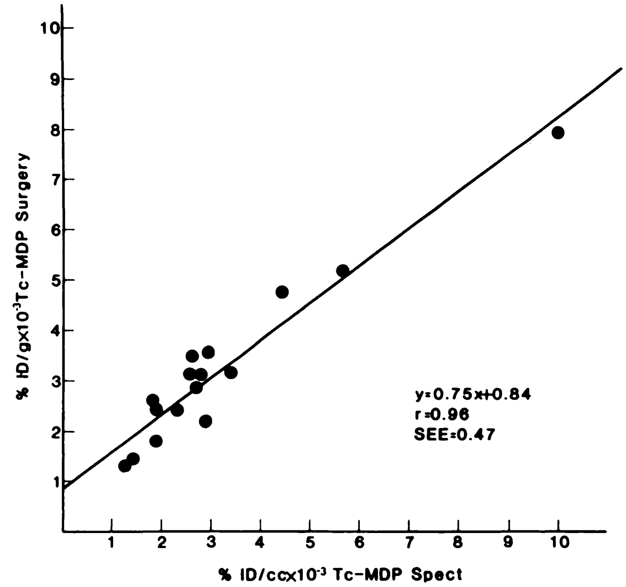


**FIGURE 2**
In vivo in vitro correlation of [$^{99m}$Tc]MDP uptake in the vault of the skull.

The interobserver difference for QBS in all bones studied was measured in 15 subjects. The QBS measurements by a senior nuclear medicine physician with a special interest in bone scintigraphy (O.I.) were compared with those of a third year nuclear medicine resident (J.J.). These observers with different experience were selected to prove the high interobserver agreement of the technique. The method is essentially automated and it is only necessary for the observer to select the slices in which the bone used for the study appears and draw a region of interest outside the boundaries of this bone (Fig. 1). The interobserver variability was evaluated by calculating the correlation coefficient between the two measurements (r) and the agreement (coefficient of repeatability) (*5*) between each pair of measurements.

The repeatability of the technique was tested by using the method suggested recently by Bland and Altman (*5*). It is expected that in a technique which shows a good repeatability 95% of the differences between two measurements will be

**TABLE 1**
Interobserver Variability in QBS Measurements

| Site | No. of patients | Mean ± s.d. (O.I.) % ID/cc × $10^{-3}$ | Mean ± s.d. (J.J.) % ID/cc × $10^{-3}$ | Coefficient of repeatability | Coefficient of correlation (r) | Linear regression |
|---|---|---|---|---|---|---|
| Rt. ilium | 15 | 4.93 ± 1.74 | 4.87 ± 1.72 | 0.31 | 0.99 | y = 1.005x + 0.03 |
| Rt. sacroiliac | 15 | 4.09 ± 1.39 | 4.19 ± 1.41 | 0.22 | 0.99 | y = 0.99x − 0.04 |
| Lumbar spine | 15 | 3.92 ± 1.49 | 3.89 ± 1.41 | 0.47 | 0.99 | y = 1.04x − 0.13 |

**TABLE 2**
Repeatability Test of Two QBS Measurements at 2 and 4 hr After Injection

| Site | No. of patients | Difference mean | Difference s.d. | Confidence limits 95% (+) | Confidence limits 95% (−) | Repeatability coefficient | Correlation coefficient |
|---|---|---|---|---|---|---|---|
| Rt. ilium | 7 | −0.31 | 0.57 | 0.22 | −0.84 | 0.85 | 0.98 |
| Rt. sacroiliac | 7 | −0.26 | 0.43 | 0.14 | −0.66 | 0.51 | 0.98 |
| Lumbar spine | 7 | −0.31 | 0.49 | 0.14 | −0.76 | 0.69 | 0.98 |
| Skull | 23 | 0.01 | 0.45 | 0.21 | −0.19 | 0.40 | 0.98 |

smaller than two standard deviations. The repeatability of QBS was measured in the same patients at different times. In seven subjects (in 23 subjects for the skull) SPECT was performed at 2 and at 4 hr after the same injection and the results were compared. In another nine patients QBS was repeated after 4 to 8 mo. Although not yet widely used, repeatability as suggested by Bland and Altman is a rigorous statistical test. We have also used the more conventional paired t-test and nonparametric tests (Sign test, Cochran Q test and Mann-Whitney U test) for comparison of the repeat studies.

## RESULTS

QBS was validated by the very good correlation found when in vivo SPECT measurements of uptake of [$^{99m}$Tc]MDP in the skull were compared with the in vitro measurements of samples of the same bone in 16 patients (r = 0.96) (Fig. 2).

A very good correlation and agreement were also found when the interobserver variability was tested in measurements of the different bones in 15 patients (Table 1). Comparisons of the left and right iliac bones and the sacroiliac regions were performed on all patients studied. A paired Student's t-test showed no significant difference between the right and left side for either the iliac bones or the sacroiliac regions. The results of the linear correlation tests were very good. The correlation coefficient for the ilium was r = 0.95 and for the sacroiliac region r = 0.96. The mean value (x $10^{-3}$) for the 130 patients included in the study was 5.87 ± 2.09 %ID/cc for the right ilium, 5.82 ± 1.98 for the left ilium, 4.83 ± 1.75 for the right sacroiliac region and 4.82 ± 1.70 for the left sacroiliac region. Measurements in seven subjects (skull was measured in 23 subjects) at 2 and 4 hr after the injection (Table 2) and in nine subjects performed after 4 to 8 mo (Table 3) showed no significant difference and a very good repeatability.

The mean uptake in the different bones investigated is shown in Table 4. There was a wide range of QBS uptake values for the same bones even in the same group age. There was a significant decrease in the mean uptake in the older age group as compared with the younger age group. In the ilium it was 6.94 ± 1.80 %ID/cc × $10^{-3}$ vs. 4.84 ± 1.70 ($p < 0.001$), in the sacroiliac region 5.39 ± 1.40 vs. 4.28 ± 1.60, ($p < 0.001$) and in the lumbar spine 4.61 ± 1.30 vs. 3.82 ± 1.40 ($p < 0.001$). Significant differences were found between the young and old age group when women and men were assessed separately. The differences were more evident in females (Table 4).

## DISCUSSION

Absolute quantitation of radiopharmaceutical uptake by SPECT using the threshold method has been shown to be highly reliable in a variety of phantoms and human tumors and tissues (*1–4*). The present study shows that it is also suitable for quantitation of [$^{99m}$Tc] MDP uptake by human bone. When in vivo patient SPECT measurements of [$^{99m}$Tc]MDP uptake in bone were compared with measurements of uptake in bone obtained at surgery from the same patient and measured in vitro in a well counter, a very good correlation (r = 0.96) was found. Good correlation between SPECT and in vitro measurements can be achieved only if two conditions are fulfilled. One, that SPECT measures accurately the concentration of [$^{99m}$Tc]MDP in the bone and the second that uptake in the bone does not vary in the 3 to 7 days period between the two studies.

Since the method is essentially automated, an excellent interobserver correlation was also found and in the individual subject there was practically no difference between the right and the left iliac bones and sacroiliac

**TABLE 3**
Repeatability Test of Two QBS Measurements Performed in the Same Patients 4 to 8 mo Apart

| Site | No. of patients | Difference mean | Difference s.d. | Confident limits 95% (+) | Confident limits 95% (−) | Repeatability coefficient | Correlation coefficient |
|---|---|---|---|---|---|---|---|
| Rt. ilium | 9 | −0.51 | 1.08 | 0.34 | −1.36 | 2.38 | 0.86 |
| Rt. sacroiliac | 9 | −0.30 | 1.02 | 0.50 | −1.11 | 2.12 | 0.91 |
| Lumbar spine | 9 | −0.27 | 0.83 | 0.39 | −0.90 | 1.75 | 0.89 |

**TABLE 4**
Quantitative Bone Scintigraphy in the Ilium, Sacroiliac Region, and Lumbar Spine in 130 Normal Subjects (% ID/cc × $10^{-3}$)

| Site | Sex | 18–26 yr No. pts | Range | Mean | s.d. | 50–85 yr No. pts | Range | Mean | s.d. | Significance of difference (p) |
|---|---|---|---|---|---|---|---|---|---|---|
| Right ilium | F | 26 | 4.07–10.50 | 7.38 | 1.43 | 36 | 1.50–8.10 | 4.57 | 1.80 | <0.001 |
| | M | 38 | 2.90–11.00 | 6.63 | 1.97 | 22 | 2.10–8.10 | 5.28 | 1.59 | <0.01 |
| Right sacroiliac | F | 26 | 3.60–7.50 | 5.55 | 1.27 | 36 | 1.90–11.00 | 4.11 | 1.82 | <0.001 |
| | M | 38 | 2.50–8.60 | 5.28 | 1.48 | 22 | 1.90–7.10 | 4.57 | 1.36 | NS |
| Lumbar spine | F | 26 | 2.50–9.00 | 4.99 | 1.28 | 37 | 1.10–7.00 | 3.76 | 1.50 | <0.001 |
| | M | 42 | 2.10–7.60 | 4.38 | 1.30 | 25 | 1.90–6.70 | 3.92 | 1.35 | NS |

regions. The results indicate that QBS measurements provide an index with high accuracy and repeatability and the method can be used reliably for clinical applications.

The method, however, has shortcomings. Potential problems could arise if QBS were used to separate different groups of patients. There is a wide range of uptake values for the same bone even in the same age group. This could pose substantial difficulties in detecting disease in the individual patient suspected of having a diffuse metabolic bone disease. The confidence with which such a patient will be detected by QBS has still to be established and is currently under investigation.

QBS shows a very good repeatability. There were no significant differences in the values obtained in the same subjects at 2 and 4 hr after the injection and in two measurements in the same subjects done 4 to 8 mo apart. It indicates that QBS is a stable and reproducible index which is not normally subject to rapid variations. It can potentially be used to monitor progression of metabolic bone diseases or response to treatment in an individual patient. QBS could be used to determine patients at risk for osteoporosis and osteomalacia, early during the course of steroid treatment, dialysis or after oophorectomy. Serial QBS studies could be used to assess the effect of treatment of these diseases, at a time when bone densitometry and quantitative computed tomography (CT) may show no significant alterations. In addition QBS has the potential for quantitation of the degree of new bone formation which occurs in woven bone in primary and secondary tumors and in osteomyelitis (*6,7*) and could be used for the evaluation of their treatment. Future progress in the field will be probably achieved by the judicious design of studies which will compare QBS in the same patient at different intervals.

The amount of uptake of MDP measured by QBS in normal bone is dependent on the regional perfusion of the bone and on the mass of remodelling bone which in turn is determined by both the mass of metabolically active bone per unit volume and the amount of remodelling that this bone mass undergoes. QBS may add a new parameter—the measurement of the remodelling of bone, to the techniques which have been traditionally used to measure bone density and bone mineral content (*8–12*). These techniques have been used to detect age related changes in an effort to diagnose osteoporosis early and find patients at risk for osteoporotic fractures (*11*). Our preliminary results show significant differences in the uptake of [$^{99m}$Tc]MDP between the normal young and old subjects in the ilium, sacroiliac region, and lumbar spine. Although these differences are superficially similar to the differences that have been shown in the studies of bone mineral density and bone mineral content (*9–11*) they are based on different mechanisms. QBS, probably, reflects the mass of remodelling bone. Dual photon absorption measurements reflect mineral content. It appears that QBS is more precise than measurements of whole-body retention of [$^{99m}$Tc]MDP (*12*), a method previously suggested for assessment of bone metabolism and response to treatment in metastatic bone disease. It permits measurements in separate bones and is not liable to artifacts such as uptake in soft tissue, kidneys, and urinary bladder.

In conclusion the results of this study indicate that QBS is an index with a very good accuracy, interobserver agreement, and repeatability. It can be used in every nuclear medicine department with a rotating camera and computer facilities. The large variations in QBS values between normal patients will probably limit the usefulness of the method to the assessment of temporal changes in an individual patient.

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