Original Article

^{99m}Tc-MIBI Whole Body Scan: A Potentially Useful Technique for Evaluating Metabolic Bone Disease

A. M. Al-Shammari, A. H. Elgazzar, Rasha A. Ashkanani

Department of Nuclear Medicine, Faculty of Medicine, Kuwait University and Mubarak Al-Kabeer Hospital, Kuwait

Abstract

Metabolic bone disease due to hyperparathyroidism is characterized by increased bone resorption and new bone formation. ^{99m}Tc- hexakis-2-methoxyisobutylisonitrile (^{99m}Tc MIBI) accumulation is controlled by metabolic function and cell viability. To investigate, for the first time, the potential of whole body ^{99m}Tc MIBI scan for detecting, visually and with the aid of quantitative analysis, bony changes associated with hyperparathyroidism. Eighty-six patients with hyperparathyroidism, referred routinely for parathyroid localization, were included in this case-control prospective study. Each patient was injected with 20-25 mCi of ^{99m}Tc MIBI. Routine anterior cervico-thoracic images were obtained for parathyroid localization. Two extra whole body images were acquired and assessed visually and by drawing regions of interest over the mandible, sternum, femur, humeri, spine, and the soft tissue adjacent to the bone. The ratios of bone to soft tissue were calculated and compared to ratios drawn in a control group routinely referred for cardiac imaging and injected with ^{99m}Tc MIBI, after confirming the absence of any bone disease. The visual interpretation of the scans showed 48 patients to have increased bone uptake. Quantitative assessment showed significant difference between the mean ratios of the case and control groups. The Kruskal-Wallis test showed significant agreement between visual and quantitative ratios drawn from delayed right and left femora and left humerus images ($P < 0.05$). ^{99m}Tc MIBI whole body imaging is a potentially useful technique for assessing metabolic bone disease associated with hyperparathyroidism. Quantitative analysis helped in confirming the visual findings.

Keywords: Hyperparathyroidism, metabolic bone disease, ^{99m}Tc- hexakis-2-methoxyisobutylisonitrile

Introduction

The term metabolic bone disease is used to describe a number of disorders that typically show either generalized or focal involvement of the skeleton as a result of disturbances in mineral metabolism. They are mostly associated with increased bone turnover and increased uptake of radiolabeled bisphosphonate. Patients usually present a challenge to diagnose on the basis of clinical and radiological findings.[1] There are multiple causes of metabolic bone disease in adults; however, the main focus in this study will be on hyperparathyroidism and renal osteodystrophy since they form the main two categories of our patients.

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Normal adult bone is constantly undergoing turnover or remodeling. This is characterized by sequences of activation of osteoclasts followed by osteoclastic bone resorption, then by osteoblastic bone formation.[2] A number of systemic and local factors regulate the process of bone remodeling. In general, factors which enhance bone resorption act by creating an imbalance between the depth of osteoclastic bone erosion and the extent of osteoblastic repair or by increasing the numbers of remodeling units which are active at any given time simply by increasing the activation frequency of bone remodeling. This results in thinning and ultimately in perforation of trabecular bone and in increased porosity of cortical bone. Systemic hormones such as parathyroid hormone (PTH), parathyroid hormone-related peptide (PTHrP), and 1,25-dihydroxyvitamin D3 (1,25(OH) 2D3) are examples of these factors which initiate osteoclastic bone resorption and increase the activation frequency of bone remodeling.[2] All of these factors have abnormal levels in hyperparathyroid and renal osteodystrophy patients.

Address for correspondence:
Dr. A. H. Elgazzar, Department of Nuclear Medicine, Kuwait University, Kuwait. E-mail: aelgazzar49@hotmail.com

Investigation of metabolic bone disease must always include measurement of calcium, phosphate, albumin, magnesium, and creatinine in serum, together with 25- hydroxyvitamin D (25OHD) and PTH.[2] Radiologic or morphological modalities, is very insensitive in detecting bone disease in patients with hyperparathyroidism, as the changes have to be severe before being radiologically detected.[3] They may show evidence of fractures, bone cysts, subperiosteal resorption of the phalanges, salt and pepper skull, brown tumors, nephrolithiasis, and bone deformity.[1] The radiographic pattern of brown tumors consists of lytic areas located in or adjacent to the bone cortex.[3]

Bone scan is sensitive in the detection of local metabolism in areas of skeletal remodeling associated with metabolic bone disease. The increased contrast between bone and soft tissues in these cases gives an appearance of excellent quality to the bone scan. In severe cases, the literature reports characteristic scintigraphic signs of increased accumulation in the long bones, increased uptake in the skull calvaria and mandible, increased uptake in the periarticular regions, decreased or nonvisualization of kidney, calcification of the soft tissue, costochondral junctions beading, and "Tie" sternum. However, these signs are only seen in latent and more advanced stages of the disease and are often nonspecific. On the other hand, in mild cases, the bone scan often is unremarkable and the detection of disease is effected by subjective interpretation.[1] Accordingly, the bone scan is uncommonly used for the detection of metabolic bone disease. Both bone and thallium-201scans were used successfully to delineate the sites of brown tumor formation. However, thallium-201 was inferior to bone scintigraphy for this purpose.[3]

Adalet, Taki, and Caner have shown increased ^{99m}Tc- hexakis-2-methoxyisobutylisonitrile (^{99m}Tc MIBI) uptake (by visual and quantitative analysis) in multiple benign bone and soft tissue lesions including giant cell tumor, neurinoma, neurilemmoma, bone cyst with fracture, enchondroma, chronic abscess, chronic osteomyelitis, diabetic foot, Sudeck's atrophy, and nonspecific fibrous tissue.[4-6] In his study, Adalet compared ^{99m}Tc MIBI uptake and Tl-201 uptake in musculoskeletal lesions and found that accumulation of both tracers in musculoskeletal lesions is not specific for malignancy.[4] Taki concluded that ^{99m}Tc MIBI is a promising radiopharmaceutical for the evaluation of these lesions.[5] ^{99m}Tc MIBI uptake seems to be more closely related to conditions such as blood flow, presence of tumor necrosis, metabolic demand, and mitochondrial activity of lesions rather than lesion status (benign or malignant).[6]

Although ^{99m}Tc MIBI accumulation in primary and secondary hyperparathyroidism was reported by many investigators in multiple case reports,[7-13] to our knowledge, no large study on the potential of ^{99m}Tc MIBI scan for imaging of various bone changes in metabolic bone disease has been performed. With these considerations in mind, this study aims to establish whether ^{99m}Tc MIBI is useful in detecting bony changes of metabolic bone disease associated with hyperparathyroidism.

Materials and Methods

This was a prospective case-control study in which two extra whole body images were acquired in patients who were routinely referred for parathyroid gland localization and in a control group selected from cardiac patients. Ethical committee approval and written informed consent was obtained prior to study. Eighty-six patients, who were routinely referred to the Department of Nuclear Medicine in Mubarak Al-Kabeer Hospital, for parathyroid scintigraphy over a period of 1 year from January 2009 to December 2009 were included in the study. All patients were proven biochemically to have hyperparathyroidism. General demographic data and medical history data (patient's age, sex, duration of disease, history of bone disease, fracture or surgery, and site of pain if any) were obtained, and all were recorded on a data sheet. The control group was compromised of 22 patient selected from patients routinely injected for rest cardiac imaging using ^{99m}Tc MIBI. For this group, patients with no parathyroid disease or renal disease and no history of bone disease, fracture, or surgery were included after a written informed consent.

Each patient was injected with 740-1110 MBq (20-30 mCi). For the patients younger than 18 years, appropriate fractional dose (based on weight and age) was used. Routine anterior cervico-thoracic, including the neck and upper two thirds of mediastinum up to the arch of aorta, images were obtained for the parathyroid localization study with a large field of view dual headed gamma camera, equipped with a high resolution parallel hole collimator (58 patients) or low energy general purpose (28 patients). Images were acquired at 15 minutes post injection and a repeat set of images were obtained at 1 and 2 hours post-injection. SPECT of the same field of view was acquired at 1 hour. While patients were waiting between the first, second, and third phases, an extra two whole body image for 15-20 minutes each were acquired for the study with no additional radiation to the patient. These images were acquired 30 minutes post injection and one and a half hour post injection. These whole body images were obtained using a movable table at a speed of 6 minutes per meter.

During a consensus review, two qualified nuclear medicine physicians, blinded to the findings of other

images of parathyroid glands analyzed the cases. Anterior and posterior views of the whole-body scan were reviewed and physicians recorded any diffuse or focal findings to establish standards of interpretation and terminology. They graded the diffuse skeletal uptake as normal, decreased, or increased. Any differences were resolved by consensus. Standard computer software option for selecting regions of interest (ROI) was used to quantify the radiotracer uptake in the mandible, sternum, spine femur, humeri, and the soft tissue in the loins region. The ratio of count of each of those regions of bone to soft tissue was calculated by dividing the average count of each region over the soft tissue [Figure 1]. These ratios were calculated in a similar manner in the control group. The data were analyzed using Statistical Package for Social Science software, SPSS version 17.

Results

Overall, 86 patients were studied 58 females (67.4%) and 28 males (32.6%) were included in the study. Their age ranged from 14 to 83 years with a mean of 46.26 ± 15.549 years. Out of the group studied, 41 (47.7%) patients had primary hyperparathyroidism, 43 patients (50%) had secondary hyperparathyroidism, and 2 (2.3%) had tertiary hyperparathyroidism. Forty-eight patients had positive bone findings on ^{99m}Tc MIBI whole body imaging. However, the remaining 38 showed no abnormalities in the skeleton. There was agreement on the findings seen in the early and delayed whole body images in all patients. The details of distribution of ^{99m}Tc MIBI uptake in the skeleton are described in Table 1. Examples of uptake in bones are shown in Figures 2 and 3.

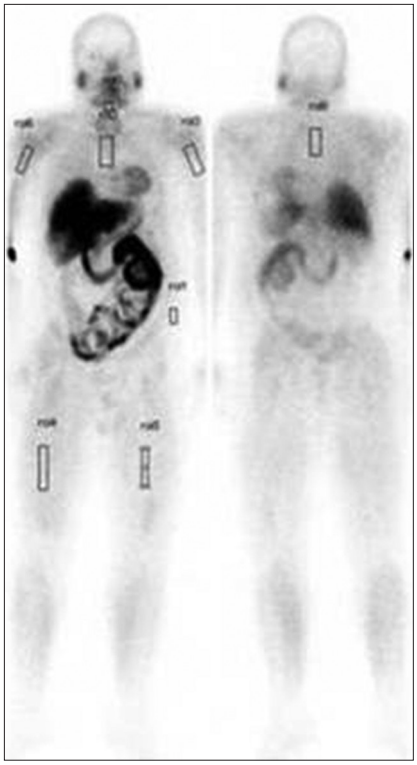

Figure 1: Regions of interest on bone and background

Among the patients imaged, eight patients had history of fractures, none of which showed tracer uptake at reported fracture sites [Figure 4]. Bone uptake on visual assessment was seen in 23 patients with primary hyperparathyroidism, 24 patients with secondary disease, and the 2 patients with tertiary disease. The Chi-square test showed no significant association between the visual assessment and type of hyperparathyroidism. However, it was noted that number of regions called on visual assessment in primary disease was less than that seen in secondary disease (average 1.9 vs. 2.25) with a lower mean level of PTH on primary disease cases associated with visual findings than the secondary disease (65.73 vs. 101.78). The number of findings called in tertiary disease was not calculated because of the small sample number.

Using the Mann-Whitney test, the early and late ratios of the long bones of the case group were significantly different from the control group ($P < 0.05$) [Table 2]. The Kruskal-Wallis test showed significant agreement between the visual findings and quantitative ratios drawn from delayed images of the right and left femur and left humerus ($P < 0.05$) in the case group with an average bone to background ratio of 2.59 for the delayed right femur, 2.51 for the left femur and 2.63 for the left humerus on quantitative analysis.

Table 1: Analysis of visual scan findings in 49 patients with positive ^{99m}Tc MIBI scan

Positive findings
Long bones 26
23 in the humerus
19 in the femur
8 in the tibia
Skull 4
Ribs 1
Sacroiliac joint 1
Mandible 1
Sternum 23
Spine 23

Table 2: Mean ratios in case and control groups at different sites at delayed images

Site	Case	Control
Sternum	3.9	3.0
Spine	4.0	2.9
Right humerus	2.9	2.1
Left humerus	2.6	1.8
Right femur	2.6	2.0
Left femur	2.5	1.9

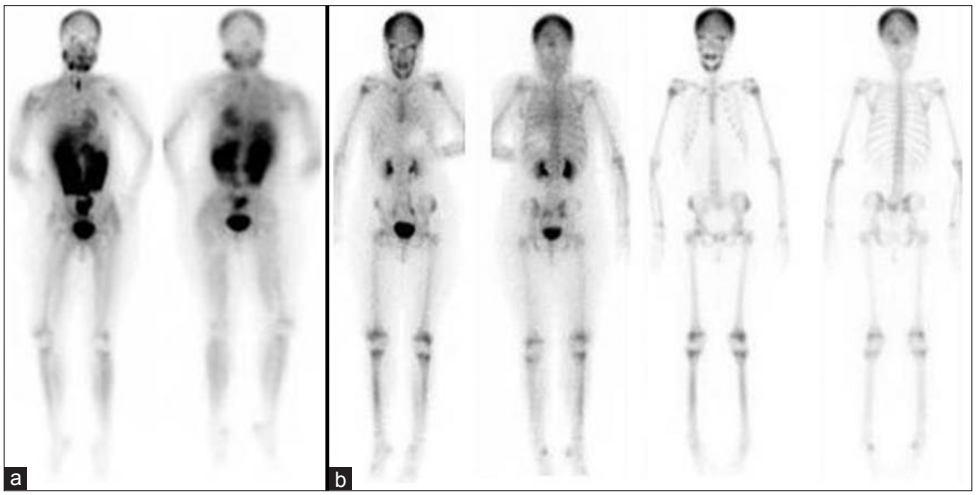

Figure 2: A 14-year-old lady with primary hyperparathyroidism. Patient had pain in the left thigh. Fractures in the left wrist, right and left forearms. Delayed whole body ^{99m}Tc MIBI scan showed uptake in the skull, long bones, mandible, and the sternum (a). ^{99m}Tc MDP bone scan showed increased radiotracer localization in the skeleton, especially the calvarium and mandible indicating metabolic bone disease (b)

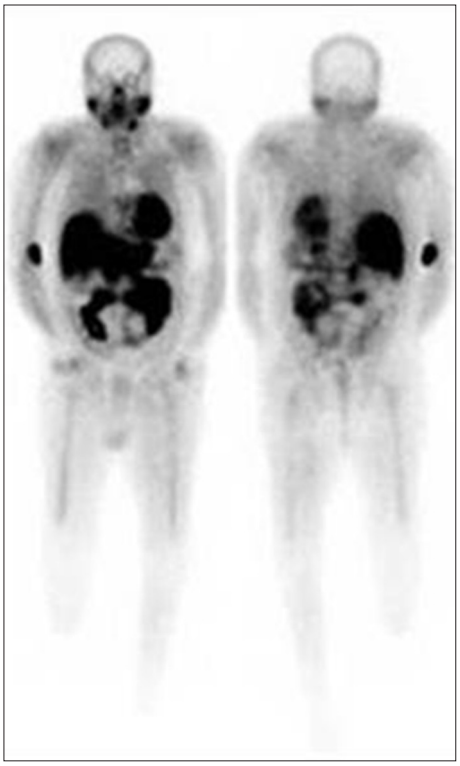

Figure 3: A 64-year-old male with secondary hyperparathyroidism with PTH of 76 pg/ml. The patient had history of arm pain for 2 months and history of fracture in 1996 in L5. Whole body delayed ^{99m}Tc MIBI scan showed uptake in long bones (humerus, radius, ulna, and femurs), and sternum

Discussion

Some radiopharmaceuticals are emerging as powerful tools to explore the function of tissues at the cellular level. ^{99m}Tc MIBI is one of the most widely evaluated representatives of this class of compounds. The reasoning behind using ^{99m}Tc MIBI in our study is that its accumulation depends on cell viability and metabolic conditions. In their study, Piwnica and his group concluded that the distribution of ^{99m}Tc MIBI *in vivo* is not only a simple function of blood flow but also represents metabolic function. They also reported that metabolic blockade could depress the tracer cellular uptake.[14] One may hypothesize that the mechanism for the increased uptake of ^{99m}Tc MIBI in a metabolic bone disease is likely to occur because of increased perfusion, metabolism, and osteoclastic activity. Also, an earlier stage in metabolic bone disease may be detected by ^{99m}Tc MIBI accumulation before the bone remodeling process, mediated by osteoblastic and osteoclastic activity, is noted on bone scan. The results presented from our data suggests that using ^{99m}Tc MIBI is useful in detecting bony changes in long bones of metabolic bone disease associated with hyperparathyroidism. Our findings were in line with other reports in the literature describing the experience with ^{99m}Tc MIBI in the context of positive imaging of benign skeletal lesions of primary and secondary hyperparathyroidism.[7-13] All of the previously mentioned studies agreed that ^{99m}Tc MIBI has the potential of detecting benign bony lesions, associated with metabolic bone disease with visual analysis. In addition, our study had shown that quantitative analysis can help confirm the visual scan findings. Similarly, Krauss and colleagues in their study to establish the value of quantification of bone uptake in metabolic bone disease on bone scan suggested the possibility of using ^{99m}Tc MIBI to detect increased bone metabolism associated with hyperparathyroidism in an earlier stage in the course of the disease.[15] In our study, there was a significant agreement between the visual and quantitative ratios drawn from late right and left femur and late left humerus only. This can be explained by that more findings were seen on the long bones than other

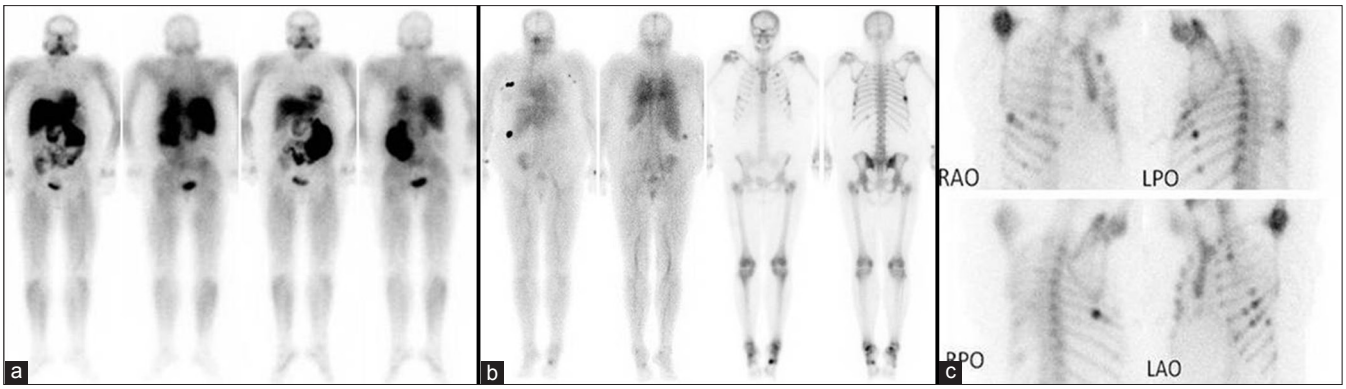

Figure 4: Traumatic fractures with positive findings on bone scan and negative on ^{99m}Tc MIBI on a 30-year-old lady with secondary HPT. PTH was 43.7 pg/ml. Patient had history of road traffic accident 5 months prior to scan. Whole body ^{99m}Tc MIBI (a) showed uptake in long bones of the upper and lower extremities. Findings of whole body ^{99m}Tc MIBI are not related to trauma. She had a bone scan, (b and c) that showed multiple focal areas of increased tracer uptake in the left 2nd, 5th, 6th, 7th, and 8th ribs, and right 7th rib at the sites of multiple fractures with no corresponding uptake on ^{99m}Tc MIBI scan

regions on the visual analysis. This may be due to the fact that it is easier to visualize those areas than the axial skeleton because of the normal physiological uptake in the heart and abdomen. The right humerus uptake may be also affected because of remnant tracer resulting from placing the cannula mostly in the right antecubital vein. In our study, eight patients who reported history of fracture following trauma had no uptake on our scan. Similarly, in his study on the potential of ^{99m}Tc MIBI for the imaging of various bone pathologies, Caner and his group found that none of the recent traumatic bone fractures had positive uptake.[6] In another study on the usefulness of ^{99m}Tc MIBI in assessing musculoskeletal tumors, all seven sites of pathological fracture showed significant uptake while no uptake was noted in three sites with simple fractures. The authors suggested that ^{99m}Tc MIBI have a potential in distinguishing between pathological and simple fractures.[16] In our study, parathyroid hormone level showed a significant association with ratios from the case group drawn on the right and left femur, right humerus, mandible, and sternum on delayed images. De Graafe found that the degree of skeletal uptake in bone scan was also related to the serum PTH levels.[17] The lower mean level of PTH in primary vs. secondary disease found in our study, together with the chronicity of secondary hyperparathyroidism may explain why a larger number of regions were noted on visual assessment in this group. Finally, some difficulties that we faced are that the prominent uptake of ^{99m}Tc MIBI in the heart and liver and the low signal to background ratio in the intrathoracic area leaves a lot to be desired in evaluating certain thoracic spine and ribs lesions. It may also be difficult to evaluate abnormal activity of ^{99m}Tc MIBI in the lumbar spine and pelvis because ^{99m}Tc MIBI activity in the gastrointestinal area and kidneys may obscure the underlying abnormality. A limitation of our study is the lack of comparison with bone scans in all patients.

Conclusion

Whole body images using ^{99m}Tc MIBI are useful in detecting bony changes in long bones of metabolic bone disease associated with hyperparathyroidism and quantitative analysis can help confirm the visual scan findings. The number of regions called on visual assessment in primary disease was less than that seen in secondary disease (average 1.9 vs. 2.25). This may indicate a stronger role for MIBI scan in secondary hyperparathyroidism patients; however, further investigation and analysis is needed to confirm these findings.

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