Quantitative bone SPECT/CT useful for selecting medical or surgery treatment in heterotopic ossification

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Abstract

Objective: Mature lamellar bone formation in extra-skeletal soft tissue is termed heterotopic ossification (HO). Surgical resection of HO is performed to preserve joint mobility, though timing is very important, as resection prior to HO maturation very often results in incomplete or inadequate excision, leading to recurrence. The present study was conducted to evaluate whether standardized uptake values (SUV) derived from quantitative bone single-photon emission computed tomography/computed tomography (SPECT/CT) are useful for assessing HO maturity and determining the appropriate timing of surgical resection. **Subjects and Methods:** Eleven quantitative bone SPECT/CT scans from six patients with HO were analyzed. **Results:** Four of the patients with a total of 10 lesions received medical treatment (bisphosphonates), and their mean SUVmax, SUVpeak, SUVmean, metabolic bone volume (MBV), and total bone uptake (TBU) values were 13.12±12.39 (range 4.41-44.35), 11.81±11.27 (4.12-40.53), 7.64±7.16 (3.02-26.05), 81.83±111.02 (15.68-290.64), and 781.30±1,301.78 (61.87-3,301.87), respectively. The two patients who underwent surgery had a total of two lesions and those mean values in those cases were 3.21±1.67 (2.03, 4.39), 2.99±1.65 (1.82, 4.15), 2.22±1.27 (1.32, 3.11), 6.77±2.21 (5.2, 8.33), and 16.39±13.46 (6.87, 25.9), respectively. Two who were evaluated with use of serial bone SPECT/CT scanning for assessment of medical treatment response showed a gradual decrease in SUV, reflecting the effectiveness of bisphosphonate therapy (SUVmax 9.01→8.94→6.11→5.37 and 6.93→5.93→4.41, respectively). **Conclusion:** Standardized uptake value derived from quantitative bone SPECT/CT scanning is useful for monitoring HO metabolic activity and determining the appropriate timing of surgical resection.

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Introduction

Heterotopic ossification (HO) is a pathological condition characterized by ectopic formation of bone in non-skeletal soft tissues. Patients with the acquired form of HO are most frequently affected by musculoskeletal trauma, or spinal cord or central nervous system injury [1, 2]. Fever, swelling, erythema, and occasionally joint tenderness are known to occur early in HO development, though can be difficult to distinguish from cellulitis, osteomyelitis, or thrombophlebitis, thus imaging modalities such as X-ray, bone scintigraphy, and computed tomography (CT) are frequently used for accurate determination. While drug therapy and surgical resection are treatment options, deciding operative intervention timing is difficult, as resection prior to HO maturation very often results in incomplete or inadequate excision, leading to recurrence. The definition of HO maturity remains difficult and inconsistent within the literature [3]. One group demonstrated that mature HO may show cancellous bone and mature lamellar bone, vessels, and bone marrow with a minor amount of hematopoiesis [4]. Serum alkaline phosphatase level cannot be used to draw clinical conclusions about maturity of HO [5]. A previous study noted that bone scintigraphy, widely employed for osteoblastic activity detection, may be useful for evaluating the maturity of HO, as well as determination of the appropriateness of medical or surgical treatment in individual patients [6].

A precise anatomical diagnosis of HO can be obtained with use of bone single-photon emission computed tomography (SPECT)/CT, which is considered superior to other imaging methods such as bone scintigraphy, radiography, and CT [7]. Moreover, several reports have noted the usefulness of quantitative values, including standardized uptake value (SUV), metabolic bone volume (MTV), and total bone uptake (TBU), derived from quantitative bone SPECT/CT findings for evaluations of bone metabolism, malignant potentiality, and treatment response [8-11]. The present study was conducted to evaluate the usefulness of standardized uptake values (SUV) derived from quantitative bone SPECT/CT for assessing HO maturity and determining the appropriate timing of surgical resection.

Subjects and Methods

Patients

Following approval from the ethics committee of our institution (No. 3144), this study was conducted in a retrospective manner. Six patients with suspected HO, based on findings obtained in various clinical and imaging examinations, underwent quantitative bone SPECT/CT examinations (total, 11 scans) between December 2019 and December 2025, and those results were analyzed. Relevant patient and lesion characteristics are shown in Table 1.

Bone scintigraphy

At three to four hours following intravenous administration of 555MBq of technetium-99m-hydroxymethylene diphosphonate (^{99m}Tc-HMDP), planar bone scintigraphy was performed using a SPECT/CT scanner (NM/CT670; GE Healthcare, Pittsburgh, Pa) equipped with a low-energy high-resolution collimator. Immediately after acquisition of planar images of the jaw region, a hybrid system was used to acquire quantitative SPECT/CT images. Initially, CT images were obtained with use of the following parameters: tube voltage 120kV, tube current 60-210mA with auto MA function (noise index 20), X-ray collimation 20mm (16×1.25mm), table speed 37mm/second, table feed per rotation 18.75mm, tube rotation time 0.5 seconds, pitch 0.938:1, and matrix size 512×512. Computed tomography images were then reconstructed into 2.5-mm-thick sections using an adaptive statistical iterative reconstruction algorithm (ASiR; GE Healthcare). Next, SPECT images were acquired using the following parameters: energy peak 140KeV with 20% window (126-154KeV), step-and-shoot acquisition mode (16 seconds/step, 60 steps/detector) with 3° angular increments, and the body contour scanning option. An additional energy window for scatter correction was set at 120KeV with a 10% window (115-125KeV). Reconstruction of SPECT images was performed using an iterative ordered subset expectation maximization algorithm (two iterations, 10 subsets) with CT-based attenuation correction, scatter correction, and resolution recovery using the software package provided by the vendor (Volumetrix MI; GE Healthcare). A post-reconstruction Butterworth filter (cut-off frequency 0.48, order of 10) was applied. Reconstructed images with a matrix size of 128×128, section thickness of 2.95 mm, and zoom factor of 1.5 were generated.

Data analysis

Volume of interest (VOI) delineation was performed by a board-certified radiologist using the GI-BONE software package (AZE Co., Ltd., Tokyo Japan), which provides quantitive parameters for SUV, such as max (SUVmax), peak (SUVpeak), and mean (SUVmean), as well as metabolic bone volume (MBV) and total bone uptake (TBU) [5-8] (Figures 1, 2). Maximum SUV represents the highest single-voxel activity within a lesion, while SUVpeak is the mean activity concentration within a 1cm^3 spherical VOI centered on the region highest uptake within an examined lesion. Mean SUV was calculated as the average SUV within the VOI, which showed uptake ≥ 40% of SUVmax. MBV represents lesion volume with uptake. SUVmean×MBV was used to calculate TBU.

Statistical analysis

Data are presented as the mean±standard deviation (SD). SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA), was used to perform statistical analysis.

Results

Eleven quantitative bone SPECT/CT scans of six HO patients were analyzed, which included four different scanning examinations for one patient and three for another (Table 1). One patient had bilateral lesions, while the remaining five each had a solitary lesion.

For all 12 lesions, mean SUVmax, SUVpeak, SUVmean, MBV, and TBU values were 11.47±11.86 (range, 2.03-44.35), 10.34±10.77 (1.82-40.53), 6.74±6.82 (1.32-26.05), 69.32±104.59 (5.2-290.64), and 653.81±1,214.57 (6.87-3,301.87), respectively. As for the 10 lesions in the four patients who underwent medical treatment (bisphosphonates), those values were 13.12±12.39 (4.41-44.35), 11.81±11.27 (4.12-40.53), 7.64±7.16 (3.02-26.05), 81.83±111.02 (15.68-290.64), and 781.30±1,301.78 (61.87-3,301.87), respectively, and for the two lesions in the two patients who received surgery were 3.21±1.67 (2.03, 4.39), 2.99±1.65 (1.82, 4.15), 2.22±1.27 (1.32, 3.11), 6.77±2.21 (5.2, 8.33), and 16.39±13.46 (6.87, 25.9), respectively. Max SUV, SUVpeak, and SUVmean values for those with drug treatment were significantly higher as compared to the surgery group (P=0.036, P=0.040, and P=0.049, respectively). Metabolic bone volume and TBU showed no significant differences between the groups.

Two patients underwent multiple bone SPECT/CT scanning sessions for analysis of medical treatment response. Both showed gradual SUV decreases, reflecting good response to treatment with bisphosphonates (SUVmax: 9.01→8.94→6.11→5.37 and 6.93→5.93→4.41). Results of two representative cases are presented in Figures 1 and 2.

Discussion

Heterotopic ossification can be classified etiologically as either hereditary or acquired. The hereditary form is rare and divided into two types; fibrodysplasia ossificans progressiva (also known as myositis ossificans progressiva) and progressive osseous heteroplasia, both of which are caused by gene mutations [12]. The more common acquired form of HO typically develops after trauma including surgery, particularly that performed along the long bones, which leads to myositis ossificans. Alternately, occurrence has been noted following an injury to the nervous system, most commonly spinal cord injury, resulting in neurogenic heterotopic ossification. Less commonly, HO may occur in association with less common conditions such as tumoral calcinosis or calcification associated with end-stage valvular disease. The pathophysiology is thougt to

Table 1. *Patient and lesion characteristics.*

Case	Age	Gender	Scan number	Time interval (months)	Location	SUVmax	SUVpeak	SUVmean	MBV	TBU	Treatment
1	31	female	1	-	rt quadriceps	44.35	40.53	26.05	19.74	514.16	Bisphosphonates
2	50	male	1	-	rt hip	20.21	17.85	10.93	290.45	3173.31	Bisphosphonates
					lt hip	19.92	17.61	11.36	290.64	3301.87	Bisphosphonates
3	36	male	1	-	lt clavicle	9.01	8.11	5.44	17.76	96.6	Bisphosphonates
			2	12	lt clavicle	8.94	8.04	5.39	15.68	81.09	Bisphosphonates
			3	21	lt clavicle	6.11	5.61	3.61	20.33	73.11	Bisphosphonates
			4	17	lt clavicle	5.37	4.89	3.26	18.87	61.87	Bisphosphonates
4	42	male	1	-	lt inguinal	6.93	5.89	3.74	49.67	185.64	Bisphosphonates
			2	5	lt inguinal	5.93	5.43	3.64	60.8	221.49	Bisphosphonates
			3	9	lt inguinal	4.41	4.12	3.02	34.36	103.82	Bisphosphonates
5	58	male	1		humerus	2.03	1.82	1.32	5.2	6.87	Surgery
6	44	female	1		lt ankle	4.39	4.15	3.11	8.33	25.90	Surgery

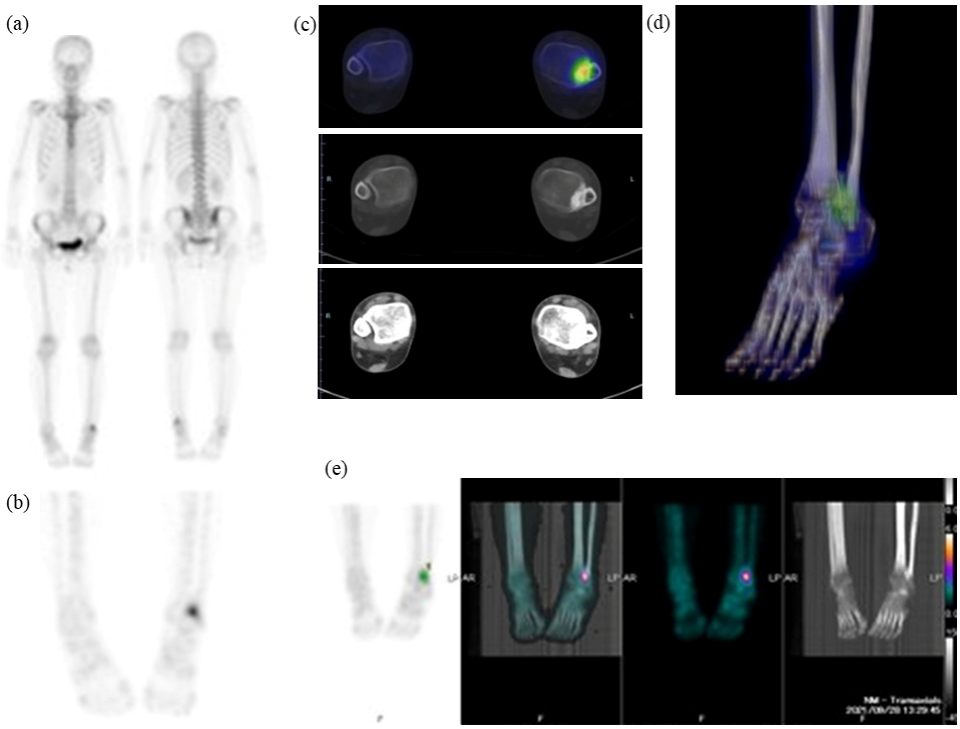

Figure 1. Representative patient; woman (44 years old) with heterotopic ossification of the left ankle. a) Planar bone scintigraphy, b) spot planar view, c) transaxial bone SPECT/CT, and d) 3D-SPECT/CT findings showing weak uptake and heterotopic ossification in the left ankle. e) VOI indicated by the GI-BONE® software package and calculated quantitative values are shown below the images: SUVmax 4.39, SUVpeak 4.15, SUVmean 3.11, MBV 8.33, and TBU 25.90. Based on the relatively low metabolic activity, surgical resection was performed.

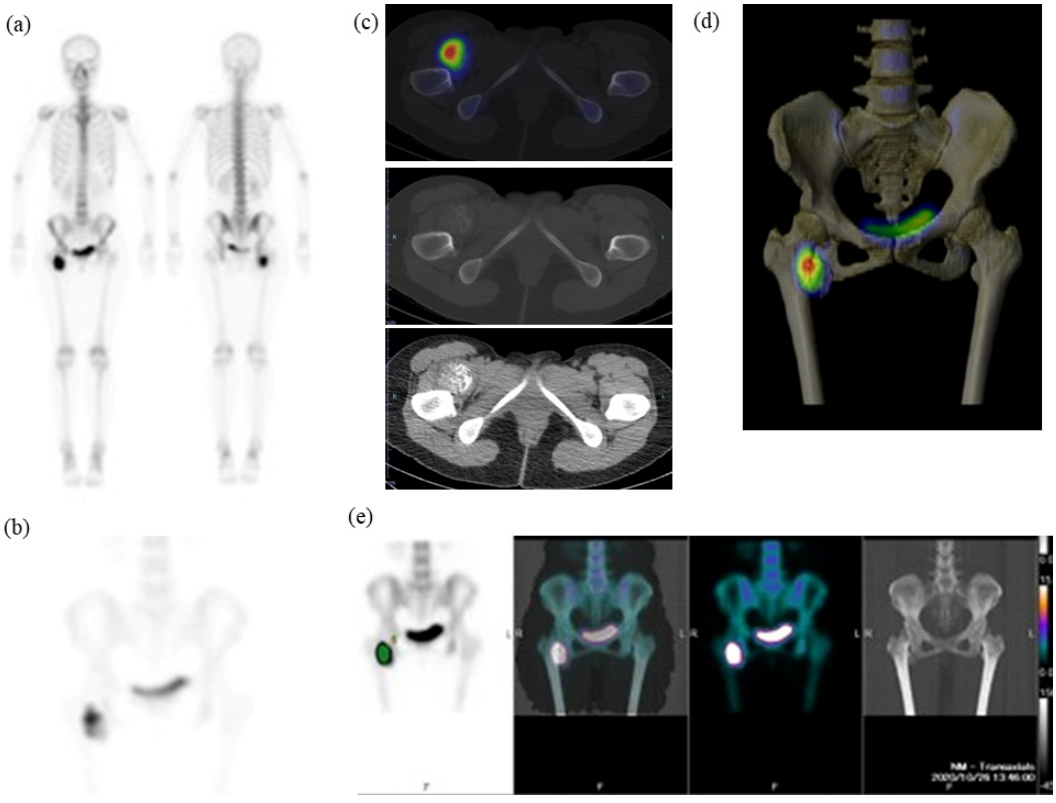

Figure 2. Representative patient; woman (31 years old) with heterotopic ossification of the right quadriceps. a) Planar bone scintigraphy, b) spot planar view, c) transaxial bone SPECT/CT, and d) 3D-SPECT/CT showing strong uptake and heterotopic ossification in the right quadriceps. e) VOI indicated by the GI-BONE® software package and calculated quantitative values are shown below the images: SUVmax 44.35, SUVpeak 40.53, SUVmean 26.05, MBV 19.74, and TBU 514.16. Based on the relatively high metabolic activity, drug treatment (bisphosphonates) was performed.

involve transformation of pluripotent mesenchymal cells within fibrous and connective tissue septa of muscle into an osteogenic cell lineage line, a process that occurs under permissive conditions or the influence of an induction agent [13]. This mechanism explains formation of heterotopic bone in affected patients at a site with some distance from normal bone, with subsequent movement towards an adjacent skeletal structure.

More than 80% of patients with acquired heterotopic bone formation show a relatively benign course. However, reports have noted significant loss of motion and ankylosis occurring in up to 10% of cases, with potential loss of function in the affected part [14-16]. Therefore, following diagnosis of early HO, interventional treatment is essential. Available therapies range from passive range-of-motion exercises, and biphosphonate and nonsteroidal anti-inflammatory drug treatment, to radiation therapy and surgical resection of mature HO, with treatment selection dependent on criteria based on clinical, laboratory, radiographic, and bone scintigraphic results. Multiphase bone scintigraphy is considered to be most useful for detecting early HO at the onset of clinical symptoms and during subsequent disease monitoring, as well as for noting maturity and determination of surgical resection timing [6]. Assessment of HO maturity is essential, because resection before maturity nearly always leads to recurrence. In addition, should excision be performed prior to heterotopic ossification maturity, incomplete and/or inadequate excision can be the result.

For assessment of HO maturity, serial semi-quantitative bone scintigraphy has been proposed, with repeated measurements of abnormal tracer uptake relative to a normal skeletal reference, such as the opposite hip, utilized [17]. Shehab et al. (2002) presented criteria for determining the necessity of surgical removal of HO if serial quantitative bone scans can be obtained, which included the following: 1) significantly limited range of motion for involved joint; 2) absence of local fever, swelling, erythema, or other clinical findings indicating acute heterotopic ossification; 3) normal serum alkaline phosphatase; and 4) return of three-phase bone scan findings to normal or near normal [6].

In a study of 12 patients with spinal cord injury, SPECT/CT was used to determine osteoblastic activity and evaluate HO maturity to identify patients at higher risk of relapse following surgical resection, with tracer uptake graded as absent, mild, moderate, or severe [18]. Lin presented findings of a patient with paraplegia that developed six months after brain injury that showed the value of SPECT/CT for determining activity and providing assistance to direct conservative management rather than surgery [19]. Additionally, the value of SPECT/CT for determining the location of abnormal activity in soft tissues surrounding the hips in a patient with Guillain-Barré syndrome was reported [20]. However, bone SPECT/CT was not used for quantitative assessment in any of these cases.

Other reports have noted use of bone scintigraphy for qualitative evaluations to assess the maturity of HO [6, 7, 17-20]. However, to the best of our knowledge, this is the first study to examine the use of quantitative values (SUV, MBV, TBU) derived from quantitative bone SPECT/CT results to evaluate HO maturation for determining medical treatment or surgery. The results indicate that a low SUVmax value (<4.4) shown by quantitative bone SPECT/CT indicates maturation, thus surgery is recommended, whereas high SUVmax (≥4.4) signals HO immaturity, indicating medical treatment. Therefore, it is considered that SUV determined from bone SPECT/CT findings are useful for not only treatment decisions, but also evaluation of bisphosphonate response in patients with HO.

Our study has several limitations. First, the number of patients analyzed was relatively small, thus limiting statistical power for determining significant associations. A prospective study that includes a greater number of subjects will be needed to verify the usefulness of quantitative bone SPECT/CT results for choosing drug or surgical treatment, especially regarding the appropriate timing of surgical resection. Additionally, comparisons with CT/MRI imaging or pathological findings were not performed.

In conclusion, use of SUV derived from quantitative bone SPECT/CT scanning are useful for monitoring the metabolic activity of HO. Additionally, they can be used to evaluate HO maturation and may be an effective evaluation tool for deciding whether to perform medical or surgery treatment, especially regarding the appropriate timing of surgical resection.

The authors declare that they have no conflicts of interest.

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