Original Article

Three phase bone scan interpretation based upon vascular endothelial response

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ABSTRACT **Objectives:** A new method of interpretation of Three Phase Bone Scan (TPBS) scan based upon the normal physiological vascular endothelial related response. **Materials and Methods:** Fifty cases of TPBS were evaluated. Thirteen were normal. In remaining 37 positive studies, 20 showed localized hyperemic response. All localized hyperemic responses except one with vascular endothelial dysfunction were without infection (95.0%). Infection could be ruled out in absence of generalized massive flow and pool response. All 17 cases with generalized massive hyperemic response had infection, consistent with infection or CRPS/RSD. Micro-bacterial or histological confirmation of infection was obtained in 11 cases. All 11 cases with confirmed infection showed generalized massive hyperemic response (100.0%). Two were CRPS/RSD and 2 cases were of cellulitis (100.0%). Among remaining 2, one refused surgery and other was lost to follow-up. Additionally, 20 published cases in the literature of osteomyelitis were also analyzed. Nineteen cases of bone and joint infection, (osteomyelitis/arthritis/cellulitis) except one with endothelial dysfunction showed generalized massive increased flow and pool response (95.0%). All published cases of osteomyelitis in the literature showed generalized massive hyperemic response (100.0%). **Results:** The data clearly indicated that 100% of the cases of bone infection (osteomyelitis/arthritis/cellulitis) and cases of CRPS/RSD showed generalized massive flow and pool pattern. Infection could be ruled out in absence of generalized massive flow and pool response. All 100% published cases of osteomyelitis in the literature showed positive vascular endothelial response. **Conclusion:** By incorporating the concept of vascular endothelial related response causing massive vasodilatation in infection, the interpretation of the TPBS can be more précised as it is based upon the normal physiology. Larger studies are recommended.

Keywords: Infection, interpretation, three phase bone scan, vascular endothelium related response

INTRODUCTION

Uptake of Technetium 99m-methylene diphosphonate (MDP) in a bone scan depends upon two factors viz. the vascularity and the local osteogenesis. Thus, there are two distinct patho-physiologies for the positivity of the bone scan, one related to the delivery of the radiotracer to the site of the lesion and other with the incorporation of the radiotracer with the hydroxyapatite crystal of the bone. Increased vascularity in infection or ischemia is the direct result of the positive vascular endothelium related response.[1] By incorporating this fact into the interpretation of the three phase bone scan (TPBS), the specificity of the TPBS can be enhanced considerably.

The increased activity noted in the first two phases of the TPBS (flow phase and the blood-pool phase) can be divided into generalized or massive increased activity spread to much larger area of the limb or localized increase in activity limited to the particular part or the region of the limb. Generalized increase in flow or pool activity, involving much larger region beyond the area of the disease process is the positive vascular endothelial depended response. The vascular endothelium being an organ with the largest surface area, the response involves a large area of the limb as noted in infection and ischemia. On the other hand, when the increased flow or pool activity is focal or limited to an area of the disease process, it is due to localized osteogenesis or neovascularization as noted in conditions such as fracture, noninfective arthritis, Charcot's joint and tumor etc., This is vascular endothelium-independent response, unless

Access this article online

Quick Response Code:

Website: www.ijnm.in

DOI: 10.4103/0972-3919.152949

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patient is also having endothelial dysfunction. Two illustrative cases, one from each group are described. This is the first study of this kind.

MATERIALS AND METHODS

Three phase bone scan was performed by injecting Technetium 99m-MDP in the upper limb while evaluating the lower limb and vice versa. General Electric Co., GE-Infinia Gamma camera was used for scanning and interpretation including for generating the time-activity curves (TACs). Procedure guideline for bone scintigraphy as proposed by Society of Nuclear Medicine, version 3, protocol was followed.

Fifty consecutive cases of TPBS of the past 2 years (2012–2013) were evaluated in the light of generalized or massive vascular endothelium-dependent and localized or focal vascular endothelium-independent flow and pool responses. Thirteen studies were normal or negative with bilateral symmetrical flow and pool patterns without any focal retention of the radiotracer in the delayed studies. Out of remaining 37 positive studies, 17 showed generalized vascular endothelium-dependent flow and pool studies and 20 showed localized vascular endothelium-independent flow and pool patterns. Among these 20 cases, 6 with arthritis, 6 with aseptic loosening of the metallic implants, 4 with traumatic remodeling fractures which included one case where infection could be ruled out following open reduction and internal fixation (ORIF) of a closed pylon fracture, 2 with bone tumors, 1 with induration, erythema and tenderness at the tip of the amputated stump with ill-fitting prosthetic socket and 1 eighty-four years old male status 4 years post total knee joint replacement with joint effusion, who was also suffering from uncontrolled diabetes mellitus (DM), erectile dysfunction and peripheral vascular disease, all features of endothelial dysfunction, showed localized flow and pool response pattern. Patient developed a sinus with frank pus discharge and died after few days with septicemia. Out of these 17 cases who showed generalized vascular endothelium-dependent flow and pool studies, 2 cases were of complex regional pain syndrome (CRPS), earlier known as reflex sympathetic dystrophy (RSD). Micro-bacterial or histological confirmation of infection was obtained in 11 cases of osteomyelitis/arthritis and in the rest of the 4 cases findings were reported as consistent with infection but confirmation of the infection could not be obtained. Two cases were of cellulitis. One case of cellulitis showed combined generalized vascular endothelium-dependent and localized vascular endothelium-independent flow and pool response having cellulitis in one extremity with Charcot's arthritis in both feet. Both these patients with cellulitis were treated empirically with broad-spectrum antibiotics without microbial confirmation with good results. Remaining 2 patients, 1 case refused surgery and 1 case was lost to follow-up [Table 1]. Quantitative interpretation of flow and pool phase of TPBS in segments of a limb by pixel counts or drawing region of interest (ROI) and developing TACs improves the precision of diagnosis

In addition, 20 published cases in the literature (journals and books of radiology and nuclear medicine) of osteomyelitis with flow, pool and delayed images of TPBS were also analyzed on the basis of vascular endothelial response. Diagnosis of osteomyelitis was established by 24 h delayed 4^{th} phase 99m-Tc MDP or hydroxyl methylene diphosphonate bone scan, 67-gallium 48–72 h delayed scan, 111-Indium white blood cell (WBC) scan, microbial culture or by tissue histology.

Two illustrative cases, one indicative of large or generalized increased flow and pool response as noted in infection (vascular endothelium-dependent response), one indicative of focal or limited increased flow and pool response as noted in fracture (vascular endothelium-independent response) are presented.

Case 1

A 62-year-old man with recent-onset DM, had left total knee replacement 3 years ago with persistent pain and swelling in the left lower extremity for the last 3 months. No definitive clinical evidence to suggest infection. Erythrocyte sedimentation rate, WBC and C-reactive protein mildly increased. The flow and the blood-pool phase images of the TPBS indicated asymmetrical pattern with generalized massive response extending up to the left malleoli, consistent with large vascular endothelium-dependent response. Delayed phase images of the TPBS indicated retention of radiotracer in the left knee bones, consistent with

Table 1: Distribution of cases

Total cases	Positive cases		Negative cases
	Generalized/massive response: 17	Localized/limited/focal response: 20	
	Confirmed infection: 11	No infection: 19 (95%)	
	Cellulitis: 2	Infection+endothelial dysfunction: 1	
	CRPS/RSD: 2		
	Lost to follow-up: 2		
	Confirmed infection+cellulitis: 13 (100%)		
50	37		13

CRPS: Complex regional pain syndrome, RSD: Reflex sympathetic dystrophy

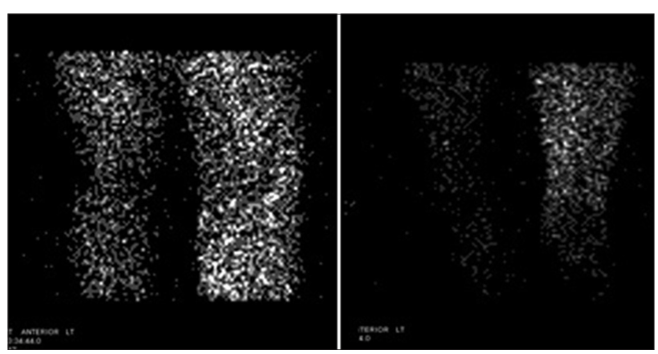

Figure 1: Flow phase of the three phase bone scan, following left arm injection of the radiotracer Technetium-99m methylene diphosphonate indicating extensive increased activity in the left lower extremity, extending from A, thigh to B, leg up to the malleoli consistent with large response

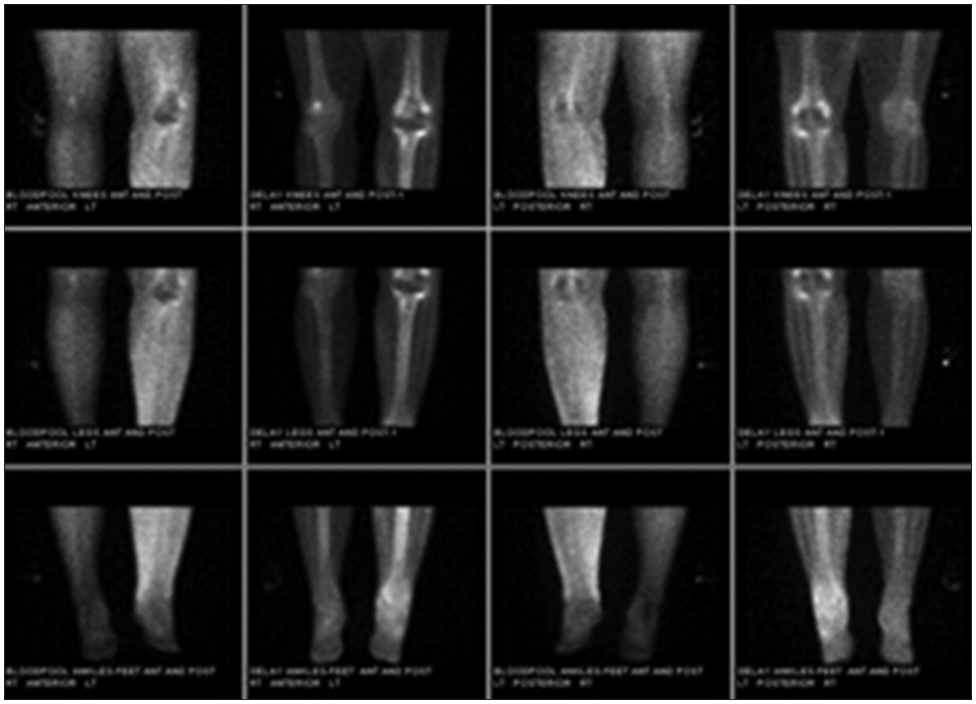

Figure 2: Blood-pool images consistent with the flow images and delayed images indicating retention of the radiotracer in the bones around the left knee, consistent with infection

infection [Figures 1 and 2]. Infection was confirmed by aspirating the injected saline. Patient was placed for 6 weeks on intravenous antibiotics with no significant improvement. Revision prosthetic replacement after total eradication of infection was planned. Till the last information, the infected total knee prosthesis was removed and replaced with antibiotic-loaded spacer with the hope to re-implant new total knee prosthesis after complete eradication of the infection. This is an example of vascular endothelium-dependent response.

Case 2

A 66-year-old male, fell on outstretched left hand and complained of pain in left wrist. Plane X-ray of the left wrist was unremarkable [Figure 3] but pain persisted. TPBS was performed on 3rd day indicated localized, limited and focal increased retention of radiotracer in flow, pool and delayed images in the region of the left wrist, consistent with fracture. The TACs drawn in the flow phase of the TPBS in different regions also confirmed it [Figures 4-6]. Second plane X-ray of the left wrist after 3 weeks of the injury confirmed intra articular fracture of the radial styloid process (Chauffeur's fracture). Patient was treated by ORIF. This is an example of vascular endothelium-independent response [Figure 7].

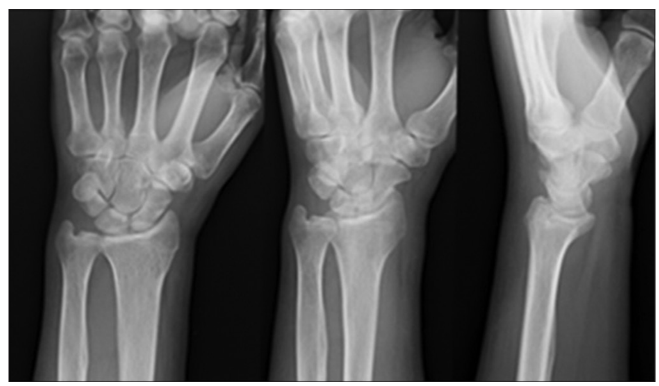

Figure 3: Post-injury X-ray of the left wrist, interpreted by the radiologist as unremarkable

RESULTS

The data clearly indicated that 100% of the cases (11 cases) of confirmed bone infection (osteomyelitis/arthritis), showed generalized vascular endothelium-dependent flow and pool studies. Similarly, 100% of the cases (2 cases) of infection (cellulitis) where bacteriological confirmation of infection was not obtained but were treated empirically with broad-spectrum antibiotics and showed good results had positive generalized vascular endothelium-dependent flow and pool studies. In 2 cases who showed positive generalized flow and pool studies and were reported as consistent with infection though bacteriological confirmation of infection was not obtained, one refused surgery, and other was lost to follow-up. All 100% of the cases (2 cases) of CRPS/RSD showed generalized vascular endothelium-dependent flow and pool studies. Infection could be ruled out in the absence of generalized massive vascular endothelium-dependent flow and pool response.

All 20 confirmed cases of osteomyelitis published in the literature showed positive generalized vascular endothelium-dependent flow and pool studies (100%). One case was reported as "Blood-pool and sequential bone scan images over left foot taken from medial and lateral aspects of ankle in patient with non healing ulcer over

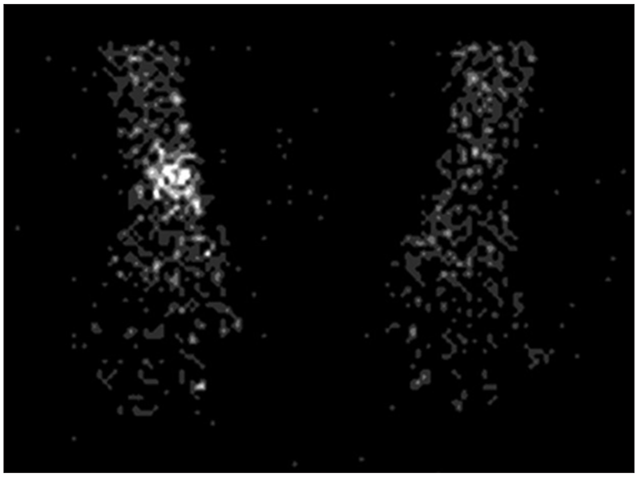

Figure 4: Flow phase of a three phase bone scan images following left leg injection of the radiotracer Technetium-99m methylene diphosphonate indicating focal increased flow in the left wrist region only

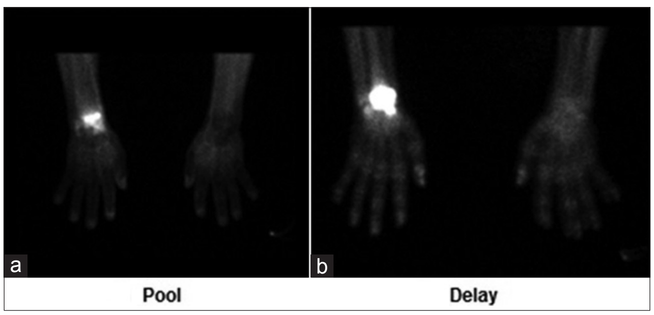

Figure 6: Blood-pool (a) and delayed images (b) indicating only focal retention of the radiotracer in the region of the left wrist, consistent with fracture and local osteogenesis

heel. Right leg has been amputated due to peripheral vascular disease. Images in the article show small hypervascular region in the heel on blood-pool image corresponding to non healing ulcer."[2] It shows a large hypervascular region not a "small hypervascular region" as stated.

By incorporating the concept of vascular endothelium related vascular endothelial response causing vasodilatation, the interpretation of the flow and pool phase of the TPBS can be divided into large/generalized vascular endothelium-dependent vasodilatation response as noted in infection and limited/focal vascular endothelium-independent response due to osteogenesis or neovascularization as noted in remodeling fracture etc., is an effective new method of interpretation of the TPBS. Patients with generalized/massive vascular endothelium-dependent vasodilatation response were consistent with the presence of infection whereas limited/focal vascular endothelium-independent response indicated no infection when vascular endothelial function was intact.

DISCUSSION

The role of nuclear medicine in diagnosing osteomyelitis was established in 1975.[3] In the same year, the role of blood-pool

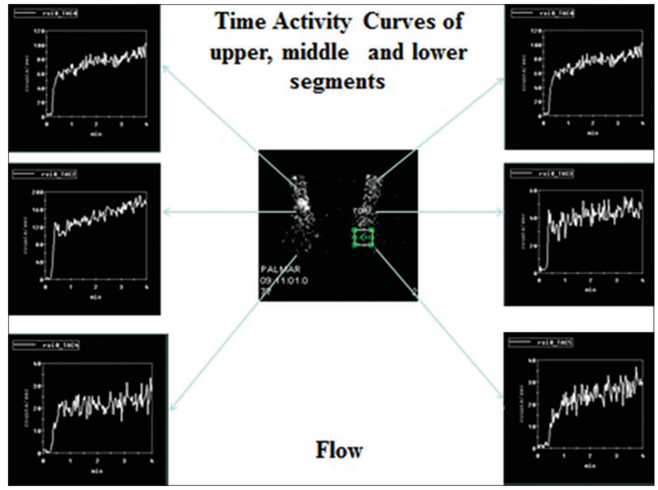

Figure 5: Time activity curves drawn on one of the flow images by placing the region of interest over proximal, distal and at the site of increased activity and distal portions of the left upper extremities confirming focal asymmetrical pattern of flow and pixel counts in the left wrist region only. The proximal and distal portions of the flow image have almost similar pattern of flow bilaterally. A pattern consistent with fracture and focal osteogenesis

Figure 7: (a) Three weeks postinjury X-ray clearly showing intra articular fracture of the radial styloid process (Chauffeur's fracture). (b) Patient was treated by ORIF

images (the tissue phase of a TPBS) was established as a part of the diagnostic criteria to distinguish cellulitis from osteomyelitis or arthritis in children.[4] Over times, other conditions were added. TPBS is 94% sensitive for osteomyelitis under all conditions and 95% specific in uncomplicated hematogenous osteomyelitis, particularly in children.[5] It also helps in differentiating between osteomyelitis and cellulitis with high specificity. However, when other conditions such as Charcot's joint, degenerative joint disease/osteoarthritis, fracture, Gout, osteotomy, osteoid osteoma and different stages of Paget's disease or of CRPS, earlier known as RSD etc., are lumped together and analyzed without making any distinction between the causative etiologies, the specificity drops down considerably. Currently, TPBS is also used in determining the vascularization and incorporation of bone grafts as well as in determining the outcome of distraction osteogenesis.[6] TPBS has very high negative predicative value but it is nonspecific in the secondary osteomyelitis.[4] WBC scan has proven to be more accurate in osteomyelitis than combined bone scan and gallium scans. TPBS in conjunction with WBC scan has a 96–100% sensitivity and specificity in diagnosing bone infection.[7] The diagnostic accuracy of bone scans improves when combined with the clinical evaluation and other radiological reports. To improve the specificity of the TPBS, it is essential to review and understand the etiology of the problems.

The first part or flow-phase of the TPBS is also known as nuclear angiography suggests increased flow of the blood to a limb or the region. Further characterization of the flow-phase is not done and hence the specificity decreases. Etiology of increased flow varies in different conditions and therefore the type or pattern of increased flow also varies in different conditions. In conditions, where increased flow is as a result of the generalized vasodilatation, the increased flow is generalized and massive involving much larger segment of the extremity such as in infection, ischemia and CRPS/RSD. "Tourniquet Effect," which is well discussed in the nuclear medicine literature[8] is a consequence of to the positive endothelial response to transient ischemia. On the other hand, when increased flow pattern is limited to a part of the extremity involving only a focal or a localized region of the extremity then the etiology is local neovascularization and hyperemia or osteogenesis, as noted in remodeling fracture, heterotrophic ossification, tumor, noninfective arthritis and Charcot's joint etc.

Vasodilatation in infection or ischemia is the direct result of the positive endothelial response. For several years, it was thought that some unknown substance was released from the vascular endothelium in infection and ischemia which caused vasodilatation as experiments on the segments of the aorta with denuded endothelium failed to dilate. This unknown substance was labeled as the "endothelium-derived relaxing factor." In 1998, the Nobel Prize in Physiology or Medicine was awarded jointly to three American Pharmacologists, Robert F. Furchgott, Louis J. Ignarro and Ferid Murad for their discoveries concerning nitric oxide (NO) as a signaling molecule in the cardiovascular system. Today it is well known that NO gas acts as a signaling molecule in regulating the blood pressure, as a weapon against infections and as a gatekeeper of blood flow to different areas of the body. When NO is released by the vascular endothelium, it diffuses rapidly through the cell membranes to the underlying muscle. The muscular contraction is turned off by the NO, resulting in vasodilatation. In this manner, NO controls the blood flow and its distribution.[9]

Vascular endothelium is the largest organ in the human body though not officially designated the status of an organ. It is present all over from head to toe, and therefore the endothelium-derived response is also quite extensive, dilating the main vessel (s) and opening the collateral circulations. It has been observed that ischemia produced in one limb may lead to the vasodilation in the other limb. Logically, it follows that in presence of infection (cellulitis or osteomyelitis), which is a common indication for a TPBS, if endothelial function is intact, the increase in flow should be extensive, involving a large segment of the limb. Thus not only the first or the flow-phase of the TPBS shows generalized increased flow but the second or the tissue-phase also indicates increased retention of the radiotracer in the soft tissues due to the increased vascular permeability and penetration of the radiotracer into the surrounding soft tissues as a result of opening of collateral circulation. The data clearly indicated that 100% of the cases with infection (osteomyelitis and cellulitis) showed positive generalized increased flow and pool response (Case 1). This is vascular endothelial-dependent response. In reverse, when the increase in the flow is localized and limited to an area of the limb, it is not caused by the vascular endothelium related response but rather by a localized neovascularization which in turn results in local hyperemia as noted during reactive bone formation (osteogenesis) in conditions like remodeling fracture, heterotrophic ossification, tumor, noninfective arthritis and Charcot's joint etc., In these conditions, flow phase indicates limited increased flow only. This is vascular endothelial independent response (Case 2).

Infection at the site of a closed fracture following surgical intervention or ORIF has always remained a challenge and great concern for the orthopedic surgeons. Often the diagnosis is difficult to ascertain, the patient continues to suffer and complains of pain without much overt clinical signs of infection. Plain radiographs may not demonstrate much or be confusing due to surgical interventions. Computed tomography (CT) scan may be difficult to interpret because of scattering due to the presence of metal and Magnetic resonance imaging is precluded. In such circumstances, clinical judgment or careful follow-up with critical serial monitoring remains the only option. A similar situation is found following total joint replacement surgery, and it often becomes difficult to differentiate between septic and aseptic loosening of the prosthetic implant. Infection usually manifests during the follow-up but often, by the time infection is detected, it becomes too late. Some recommend empirical use of antibiotics in such situations, though it may not be a very scientific approach and has its own consequences. TPBS may often be crucial in such situations, particularly at places where facility for WBC scan may not be readily available.

Three phase bone scan is a comparative study between normal and abnormal sides. In cases, where both the limbs are involved in the disease process or where only one limb is available for the study, the evaluation may be compromised and not very reliable. Generally visual interpretation of the dynamic flow part of the three-phase bone scan is adequate for interpretation by trained eyes. Quantitative interpretation of the first two parts of the three-phase bone scan in segments of the limb (proximal/middle/distal), either by pixel counts or by drawing ROI and developing the TAC will certainly improve the quality of the interpretation and also narrow the differential diagnosis.[10] In the presence of infection, all (proximal, middle and distal) segments will have increased counts indicating generalized hyperemia whereas in noninfective situations like a remodeling fracture, fracture with ORIF or aseptic loosening of the prosthetic implants, only the concerned segment will have increased counts indicating focal hyperemia due to focal

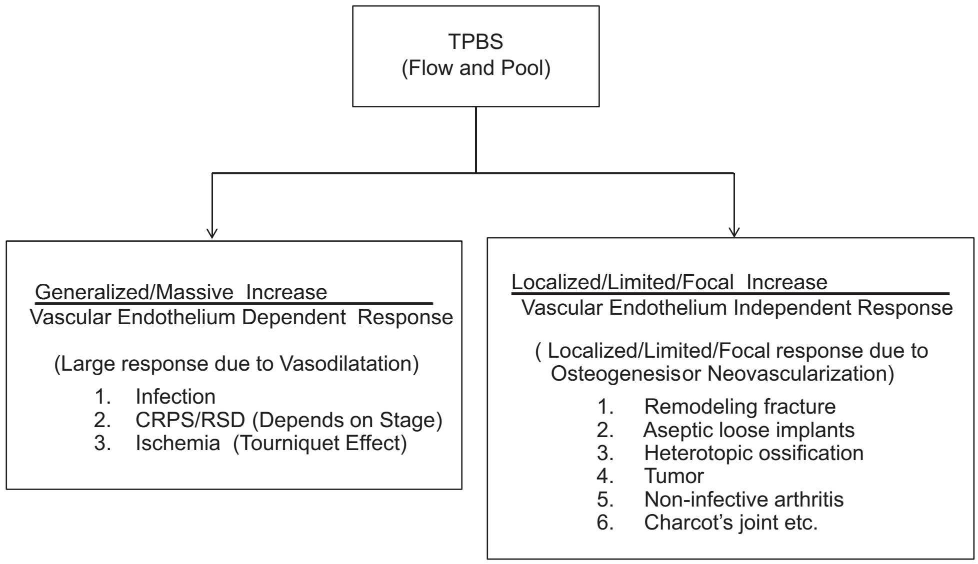

Figure 8: A proposed new classification to interpret three phase bone scan

osteogenesis and neovascularization, unless patient is also having vascular endothelial dysfunction. A four phase bone scan may slightly increase the accuracy of the interpretation in assessing osteomyelitis in patients with peripheral vascular disease from 80% to 85%[2] but is not commonly practiced, probably because four-phase study was noted only "slightly better than three-phase." No logical explanation for this slightly better result was provided. Technetium-99m phosphate uptake in bone depends upon the bone blood flow[10] and osteogenic activity. Both these factors remain the same in the third and fourth phase of the bone scans. The only factor which may "slightly" change is the background clearance of the radiotracer from the soft tissues and probably slightly improving the visual contrast. The four phase bone scan concept is also based upon very week scientific grounds that uptake of Technetium-99m MDP stops at about 4 h in lamellar bone and continues for about 24 h in woven bone (abnormal bone around osteomyelitis and bone tumors).[11,12] The protocol for the fourth phase bone scan is also very inconvenient to the patients, hence not popular. Soft tissue clearance may be delayed in patients with peripheral vascular disease and in such situations; extended delayed images may provide better tissue contrast.[13] In CRPS/RSD, increased, decreased or normal uptake of the radiotracer is dependent upon the stage of the disease.[14]

Variations are not uncommon in medicine. Our rainbow has black and brown colors also. Sometimes it may be difficult to exclude infection in acute fracture due to associated extensive traumatic inflammation producing positive large response on the flow-phase and the tissue-phase of the TPBS study. However, with the passage of time and stabilization of the fracture, the traumatic, inflammatory response subsides and the limited focal hyperemia picture emerges. Conversely, in states of poor vascularity with compromised delivery of the radiotracer, low-grade chronic infection, very early phase of infection, in bilateral limb infections as often noted in bilateral diabetic/neuropathic feet or in persons with endothelial dysfunction, which often presents clinically by associated erectile dysfunction, the classical extensive flow and tissue phase response involving large and massive areas may not be present and clear distinction between infection or no infection may be difficult. The matter compounds and becomes yet more difficult when two or more pathologies exist together. A new classification to interpret TPBS is described in Figure 8.[15] This is the first study connecting TPBS interpretation based on the vascular endothelial response. Larger studies with different common pathologies and different combinations of pathologies will help answering some of these questions.

CONCLUSION

Visual or quantitative segmental evaluation of the TPBS by drawing ROI and developing TAC is based upon the normal physiological reaction to the etiology of the disease process, that is, vascular endothelium-dependent response or vascular endothelium-independent response. TPBS interpretation based on this novel idea improves the diagnosis of infective and noninfective bone/joint diseases. Generalized or massive hyperemia supports infection. This is the first study about this concept. Larger studies are required to cover different permutations and combination of clinical scenario and pathologies.

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How to cite this article: Kumar K. Three phase bone scan interpretation based upon vascular endothelial response. Indian J Nucl Med 2015;30:104-10.

Source of Support: Nil. **Conflict of Interest:** None declared.