Semiquantitative Skull Planar and SPECT Bone Scintigraphy in Diabetic Patients: Differentiation of Necrotizing (Malignant) External Otitis from Severe External Otitis

Ruth Hardoff, Sara Gips, Nechama Uri, Avi Front and Ada Tamir

Departments of Nuclear Medicine, Otolaryngology and Community Medicine and Epidemiology, Carmel Medical Center and the Faculty of Medicine, Technion—Israel Institute of Technology, Haifa, Israel

Early diagnosis of necrotizing external otitis (NEO) includes the use of bone scintigraphy since clinical assessment alone cannot differentiate the necrotizing type of otitis from the severe type of external otitis in which there is no extension to the adjacent bone. Four-hour planar bone scintigraphy may reflect soft-tissue infection, and therefore may not be useful in distinguishing NEO from severe external otitis (SEO). Twenty-four-hour bone scintigraphy using planar or SPECT imaging may better reflect bone uptake and increase the accuracy of the test. **Methods:** Twenty-six diabetic patients (12 diagnosed NEO; 14 SEO) and 10 nondiabetic (ND) patients were studied. Lesion-to-nonlesion (L/N) count ratios obtained from planar and SPECT imaging at 4 hr, 24 hr and 24 hr/4 hr (24/4) were assessed. **Results:** Count ratios obtained from the 4- and 24-hr planar and SPECT images were significantly higher in the NEO patients compared to SEO patients for both planar and SPECT studies ($p < 0.001$, 0.005). The 24/4 count ratio was also significantly higher in the NEO patients on the planar ($p < 0.01$) and the SPECT studies ($p < 0.001$). The ND patients were not different from SEO patients on 4-hr planar, 4- and 24-hr SPECT as well as 24/4-hr planar and SPECT studies. The L/N count ratio threshold yielding the best sensitivity for detecting NEO was 1.05 for the 24/4 SPECT study. **Conclusion:** In diabetic patients, an early distinction between NEO and SEO patients can be reliably made by using L/N count ratios on 24/4 or 24-hr SPECT bone scintigraphy.

Key Words: otitis externa; diabetes mellitus; bone imaging; radionuclide imaging; SPECT; semiquantitation

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Necrotizing external otitis (NEO) is a fulminant Pseudomonas infection of the external auditory canal affecting mainly elderly diabetic patients. These patients fail to respond to topical treatment and the infection may spread from the external ear canal to adjacent soft and bony tissues resulting in multiple cranial nerve involvement and skull osteomylitis. NEO was first described by Meltzer and Kelemen (*1*) in 1959. Since then new diagnostic and therapeutic measures have been developed, improving the prognosis of this severe illness. With the increase in the longevity of diabetic patients, the prevalence of patients who are suspected of NEO has also increased (*2*). It has been noticed that a group of these elderly diabetic patients who present with all the characteristics of NEO, may in fact have a benign course of the disease with involvement of the external ear without the development of temporal bone osteomyelitis. These patients are classified as severe external otitis (SEO) and require treatment for shorter periods of time.

We have previously shown that lesion-to-nonlesion (L/N) count ratios obtained from ^{99m}Tc-labeled methylene diphosphonate (MDP) planar bone scintigraphy could distinguish between patients with NEO and SEO (*3*). Since planar images are a sum of uptake from all tissues imaged, it may be possible that 4-hr planar bone scintigraphy may include uptake from bony structures and inflamed soft tissues as well (*4*), and that single-photon emission computed tomography (SPECT), may therefore better differentiate between uptake in soft tissues and inner skull bony structures (*5*). The increase in L/N count ratios calculated from 4-hr and from 24-hr bone scintigraphy (24/4 count ratio), has been shown to differentiate between osteomyelitis and soft tissue infection (*6*). The objectives of this study were to compare L/N count ratios derived from 4-hr ^{99m}Tc-MDP planar images with 4-hr SPECT images, and to assess whether planar and SPECT 24-hr scintigraphy and 24/4 count ratios, either planar or SPECT, may increase the sensitivity and specificity of the test for detection of temporal bone osteomyelitis in patients with NEO.

METHODS

Patients

A prospective study carried out from November 1989 through December 1992 included 26 consecutive diabetic patients with

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For correspondence or reprints contact: Ruth Hardoff, MD, DSc, Dept. of Nuclear Medicine, Carmel Medical Center, 7 Michal St., Haifa 34362, Israel.

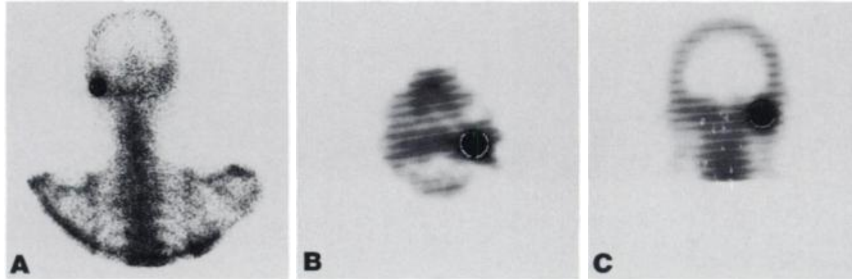

FIGURE 1. Circular ROIs drawn around areas of increased MDP uptake (L), at 4 hr postinjection, on the posterior planar view (A) and on the SPECT transaxial (B) and coronal (C) slices. The counts within each region are recorded and the same region is then moved to the unaffected side (N). L/N can then be calculated.

severe external ear infection resistant to conventional antibiotic therapy. Ten nondiabetic (ND) patients with severe external ear infection were also examined. All patients were initially treated in an outpatient clinic affiliated with the hospital and in primary outpatient clinics in the community and were referred to the hospital due to nonresponse to treatment. The inclusion criterion for entry into the study was nonresponse to treatment of external otitis for at least 3 wk with topical application of ear drops and oral antibiotics. Patients with recent infection within 6 mo, NEO or SEO, bilateral NEO or chronic otitis media, were excluded from the study.

On admission, patients were examined, their ear lesions recorded, and cultures were obtained from the external ear canal. Four- and 24-hr ^{99m}Tc-MDP planar and SPECT bone scintigraphy was performed prior to any further treatment. Patient management following scintigraphy consisted of intravenous administration of mezlocilline, oral administration of ciprofloxacin, as well as topical application of ear drops and surgical debridement of granulation tissue when present (7). Patients responding to treatment within 1 wk, demonstrating decrease of edema and pain and having negative ear cultures, were classified as SEO. These patients were discharged from the hospital and therapy was continued at home with oral ciprofloxacin. Patients who demonstrated both persistent ear edema and positive Pseudomonas cultures despite treatment were classified as NEO. Intravenous antibiotic therapy was administered until complete recovery followed by oral therapy for a total of 6 wk (*8,9*). The ND patients were treated in the same manner as the SEO patients.

Bone Scintigraphy

Patients were injected intravenously with 20 mCi of ^{99m}Tc-MDP (Soreq Nuclear Plants, Yavneh, Israel); scintigraphy was performed 4 and 24 hr later, using a large field of view gamma camera interfaced with a dedicated computer (Apex 009, Elscint Ltd., Haifa, Israel) and fitted with an all-purpose, parallel-hole collimator. A 10% window was used centered on the 140-keV photo peak. Anterior, right lateral, left lateral and posterior skull views were obtained using 256 × 256 matrix size collecting 600 × 10^3 counts per view. For the 24-hr planar images, 300 × 10^3 counts were collected. Four-hour skull SPECT studies were performed using a 64 × 64 matrix, with 15% window, collecting images each 3° for 360° for 20 min resulting in 4000–4200 × 10^3 counts per study. The 24-hr study was performed in a similar manner, except for using 6-degree frames resulting in 250–430 × 10^3 counts per study. The raw data were backprojected using a normal Hanning (1:1) filter to form transaxial and coronal tomograms of 0.688 cm thickness per slice which encompassed the entire skull. No attenuation or scatter correction were used.

Image Analysis

Image analysis was carried out independently by two experienced observers (RH, SG) at the end of each study. For the planar images, the posterior view was used. A circular region of interest (ROI) measuring 100–156 pixels was drawn within the area of the mastoid, where increased tracer uptake was noted (L) (Fig. 1A). The same ROI was moved to the nonaffected side (N) and the counts in both sides were recorded (*3*). A lesion-to-nonlesion ratio (L/N) was then calculated. In addition, a 24-hr/4-hr (24/4) ratio [L/N (24 hr)/L/N (4 hr)] was also calculated (*6*). For the SPECT studies, a circular ROI was used measuring 17–23 pixels. The slice used for analysis was the slice in which the increased uptake was most prominent and remained evident when counts were subtracted from the images (using a background dial), which caused the rest of the images to disappear. For the SPECT studies, both transaxial and coronal slices were analyzed (Figs. 1B and C) and the highest ratio of the two measurements was recorded. This was done assuming that the slice showing the highest L/N ratio was probably the closest to the infected site, while other slices showing lower count ratios were located in the periphery of the process. The intraobserver and interobserver variabilities were assessed using linear regression analysis, and testing that the slope was 1 and the intercept was 0. A nonparametric Kruskal-Wallis test was used in order to compare count ratios of NEO, SEO and ND patients. A receiver-operating characteristic curve (ROC) analysis was used to determine the L/N ratio values for which the best sensitivity and specificity was observed.

RESULTS

Clinical Data

Of 26 diabetic patients with a mean age of 61 ± 18.2 yr (range 22–81 yr), 15 were males. Edema of the ear canal, pus and positive Pseudomonas cultures were present in all patients, and granulation tissue was observed in 12.

Fourteen patients responded to treatment within the first week by a decrease in the external ear edema and pain, and their ear cultures turned negative. These patients were classified as SEO and were treated topically and with oral ciprofloxacin. Twelve patients who did not improve within 1 wk, and presented with persistent ear edema and a positive Pseudomonas culture, were considered as suffering from NEO and were administered prolonged antibiotic therapy. A characteristic case of a patient with NEO is presented in Figure 2. None of these patients developed cranial nerve neuropathy. Computed tomography was performed in 17 of the diabetic patients and became abnormal in 3 of the NEO patients.

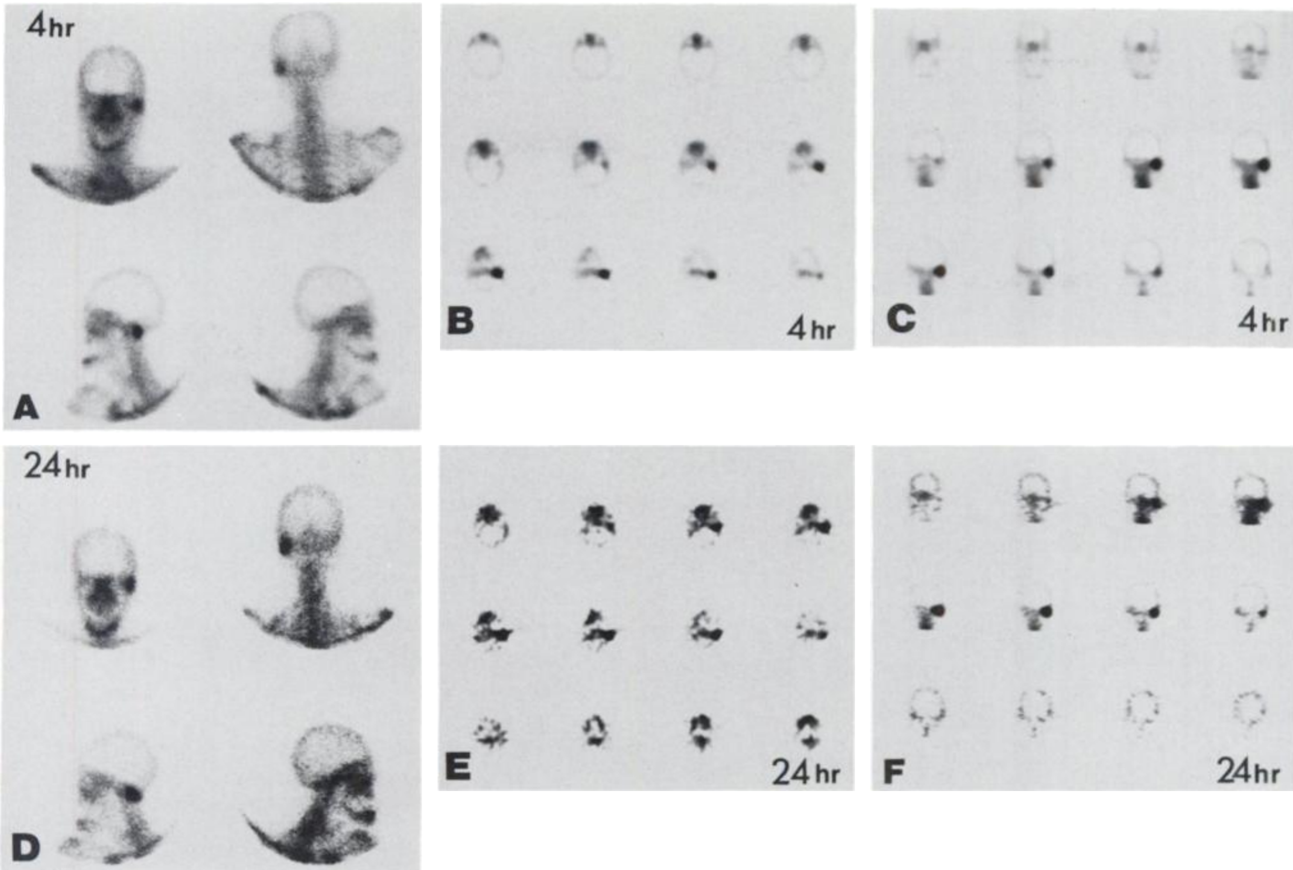

FIGURE 2. Four- and 24-hour planar and SPECT images of a 66-yr-old diabetic male patient with NEO (same patient as in Fig. 1). The patient presented with a painful left ear and pus discharge which was unsuccessfully treated for 3 wk with ciprofloxacin. On admission, severe edema and granulation tissue were observed and culture yielded Pseudomonas. Computed tomography of the skull was normal. Planar 4-hr (A) and 24-hr (D) bone scintigraphy showed increased uptake in the left temporal bone with L/N of 3.8 and 4.06, respectively and a 24/4-hr count ratio of 1.06. Four- and 24-hr transaxial (B, E) and coronal slices (C, F) generated from the SPECT studies. The highest L/N count ratios were found on the coronal slices: 4 hr: 3.8; 24 hr: 4.4; 24/4: 1.15. The patient required four local debridement procedures and prolonged intravenous administration of antibiotic therapy.

The 10 ND patients were 35.7 ± 8.7 yr old and three were male. They all had pus and edema in the external auditory canal as well as positive Pseudomonas cultures, but without granulation tissue. All these patients responded to therapy within 1 wk.

Semiquantitative Scintigraphic Results

The results of the intra- and interobserver variation of the count ratios determination of the planar and SPECT imaging are shown in Table 1. Good intraobserver correlations (r = 0.985–0.997) and interobserver correlations (r = 0.994–0.988) were found for both the planar and the SPECT imaging. All slopes and intercepts did not differ significantly from 1 and 0, respectively.

Figures 3 and 4 describe the L/N count ratios of the three groups of patients obtained from planar and SPECT images at 4 and 24 hr, and Table 2 summarizes the average count ratios of these groups as well as the 24/4-hr count ratios. Four-, 24- and 24/4-hr count ratios from planar images of the NEO and SEO patients, and count ratios from NEO and ND patients were significantly different, while the SEO and ND patients did not differ. The results from the SPECT studies were similar, except for the 4-hr SPECT study which was significantly different in comparing SEO and ND patients (Table 3).

TABLE 1
Observer Variability for L/N Count Ratio Determination

Imaging technique	r	y	p
Intraobserver variability			
Planar (4 hr)	0.997	0.973x + 0.024	<0.001
Planar (24 hr)	0.994	1.049x + 0.067	<0.001
SPECT (4 hr)	0.997	0.997x + 0.013	<0.001
SPECT (24 hr)	0.985	0.985x + 0.008	<0.001
Interobserver variability			
Planar (4 hr)	0.994	0.929x + 0.070	<0.001
Planar (24 hr)	0.997	1.041x − 0.081	<0.001
SPECT (4 hr)	0.995	1.010x − 0.022	<0.001
SPECT (24 hr)	0.988	1.023x − 0.089	<0.001

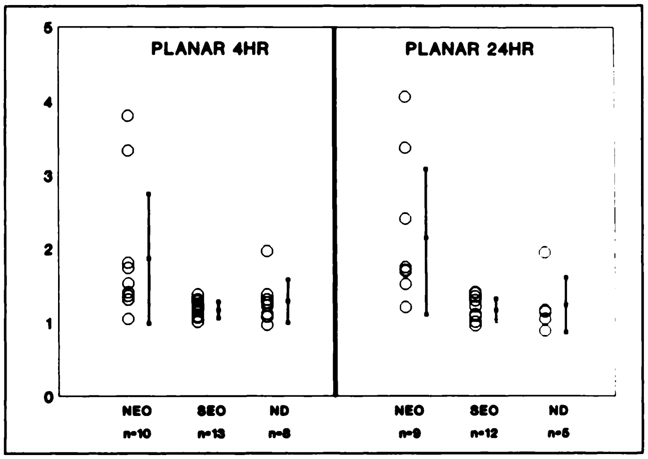

FIGURE 3. Four- and 24-hr planar lesion-to-nonlesion count ratios obtained from NEO, SEO and NDs.

ROC analysis of the 4-, 24-, and 24/4-hr count ratios for both the planar and SPECT images selected thresholds above which these ratios showed the best sensitivity and specificity for the diagnosis of NEO (Table 4). A count ratio threshold of 1.94 obtained with 24-hr SPECT yielded a sensitivity of 92% and specificity of 83%. For the 24/4-hr SPECT imaging, a count ratio threshold of 1.05 was selected, yielding a sensitivity of 100% and a specificity of 67%. Count ratios obtained from planar images and 4-hr SPECT images yielded inferior results.

DISCUSSION

Radionuclide bone scintigraphy has been widely used for the early detection of NEO (*10,11*), and was found to be superior to radiography. Periostal reaction and bone formation may progress slowly in diabetic patients, therefore the radiographic changes are even less sensitive in diabetics compared to nondiabetics (*12*). In spite of the sensitivity of bone scintigraphy for the detection of temporal bone osteomyelitis due to necrotizing otitis, uptake of the bone-seeking radionuclide depends not only on the osteoblastic activity of the lesion, but also on the uptake in the soft inflammatory process in which hyperemia and blood vessel permeability occur. Soft tissue uptake is especially difficult to assess in diabetic patients (*12*), and even techniques such as four-phase bone scintigraphy cannot always determine whether ^{99m}Tc-MDP uptake in an inflammatory process adjacent to bony structures, is due to soft tissue uptake or incorporation of the bone-seeking agent into bone, indicating osteoblastic activity (*13*).

It has been suggested that around an active bone process, such as osteomyelitis and metastatic bone lesion, a new woven bone develops (*14*), causing continuous ^{99m}Tc-MDP uptake beyond the conventional 3–4 hr postinjection when bone scintigraphy is usually performed. This continuous process may be utilized to differentiate necrotizing external otitis involving bony structures from severe external otitis which is limited to soft tissues of the external auditory canal.

Israel et al. (*6*) have shown that a 24/4-hr count ratio of 1.06 resulted in a sensitivity of 82% and specificity of 92% for the detection of osteomyelitis. In their group, only two diabetic patients were included and therefore it is unclear whether diabetic patients demonstrate different MDP kinetics over time. Diabetic patients suffer from microangiopathy which leads to the development of thick collagen extending from the cartilage to the dermis of the external ear canal. This vascular compromised tissue is susceptible to the invasion of opportunistic organisms and may be

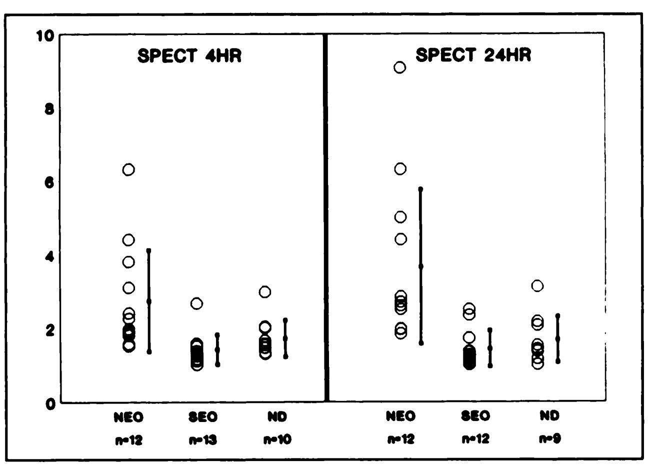

FIGURE 4. Four- and 24-hr SPECT lesion-to-nonlesion count ratios obtained from NEO, SEO and NDs.

TABLE 2
Patient Population L/N Count Ratios

Group	Planar imaging n	mean	s.d.	SPECT imaging n	mean	s.d.
NEO (4 hr)	10	1.86	0.88	12	2.74	1.38
SEO (4 hr)	13	1.16	0.11	13	1.41	0.40
ND (4 hr)	8	1.28	0.29	10	1.71	0.49
NEO (24 hr)	9	2.14	1.00	12	3.66	2.09
SEO (24 hr)	12	1.16	0.15	12	1.43	0.48
ND (24 hr)	5	1.23	0.37	9	1.68	0.62
NEO (24/4)	9	1.25	0.28	12	1.31	0.17
SEO (24/4)	11	1.02	0.06	12	1.03	0.19
ND (24/4)	5	0.94	0.07	9	0.96	0.11

TABLE 3
Statistical Significance Between the Different Patients Groups

Imaging technique	Compared groups	p Value 4 hr	24 hr	24/4
Planar	NEO, SEO	<0.001	<0.001	<0.01
Planar	NEO, ND	<0.05	<0.01	<0.001
Planar	SEO, ND	N.S.	N.S.	N.S.
Planar	NEO, SEO, ND	<0.01	<0.01	<0.01
SPECT	NEO, SEO	<0.001	<0.005	<0.001
SPECT	NEO, ND	<0.01	<0.001	N.S.
SPECT	NEO, SEO, ND	<0.001	<0.001	<0.001

TABLE 4
Receiver Operator Curve Analysis of L/N Count Ratios of NEO and SEO Patients

Imaging technique	n	Thresh	FP	TN	TP	FN	Sens	Spec	Accu	PPV	NPV
Planar (4 hr)	23	1.35	1	12	8	2	80	92	87	89	86
Planar (24 hr)	20	1.50	0	11	7	2	78	100	90	100	85
Planar (24/4)	20	1.10	1	10	7	2	78	91	85	88	83
SPECT (4 hr)	25	1.79	1	12	10	2	83	92	88	91	86
SPECT (24 hr)	24	1.94	2	10	11	1	92	83	88	85	91
SPECT (24/4)	24	1.05	4	8	12	0	100	67	83	75	100

Thresh = threshold; FP = false-positive; TN = true-negative; TP = true-positive; FN = false-negative; Sens = sensitivity; Spec = specificity; Accu = accuracy; PPV = positive predictive value; and NPV = negative predictive value.

refractory to treatment due to multiple factors such as reduced blood flow and oxygenation (*15*), malfunction of the diabetic polymorphonuclear leukocytes characterized by poor migration, and reduced chemotaxis and phagocytotic activity (*16*). Although we did not observe reduced MDP uptake in our previous study and all NEO patients had increased L/N count ratios on 4-hr planar imaging (*3*), microangiopathy and possible reduced blood flow may have been responsible for the reduced uptake observed in a few of the NEO patients in the present series.

It is possible that infection-seeking agents such as ^{67}Ga- or ^{111}In-labeled white blood cells may have been more sensitive in the detection of infection, however, they cannot differentiate between soft tissue and bone involvement. After making the diagnosis of NEO, both agents are recommended for follow-up (*17*) since bone scintigraphy remains positive for an extended period of time (*17,18*).

Count ratios obtained from the planar imaging and the 4-hr SPECT imaging were not sensitive enough in detecting NEO patients when using the best threshold selected by the ROC analysis. The main reason for this is that two NEO patients had low 4-hr ^{99m}Tc-MDP uptake, causing them to be read (using the best thresholds) as false-negatives. SPECT imaging at 24-hr using 1.94 count ratio threshold correctly identified one of them and the 24/4-hr SPECT correctly identified both of them. This was achieved by reducing the specificity of this threshold. A hypothetical explanation for these results may be the differences in the rate of bone uptake of diabetics and nondiabetics. While nondiabetics demonstrate prompt MDP uptake and fast washout in soft tissue infection without bone involvement, diabetics may show reduced uptake, either with or without bone involvement due to microangiopathy. Therefore, the prolonged continuous uptake in the newly formed bone around the inflammatory process expressed by the 24-hr and by the 24/4-hr count ratio, may help in identifying NEO patients, even if their 4-hr MDP uptake is reduced.

We conclude that 24-hr SPECT L/N count ratio of 1.94 is the best validity parameter, although it missed one NEO patient. Despite the low specificity of count ratio threshold of 1.05 obtained from 24/4-hr SPECT which would result in the unnecessary prolonged treatment of several SEO patients, it seems to be the parameter of choice since no NEO patient would be missed using this threshold. Since NEO is not a prevalent disease entity and we could identify only 12 patients within 3 yr, it is necessary to validate our findings in a larger diabetic patient population.

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