Abstract. – Background: The diagnosis of spondylodiscitis can be difficult, because the patient's history, subjective symptoms and physical findings are often inconclusive, particularly in the early stages.

Aim: To perform an overview on the role of nuclear medicine procedures with single photon emission tomography (SPET) and positron emission tomography (PET) tracers in the diagnosis of spondylodiscitis.

Materials and Methods: A literature review about bone scintigraphy, Gallium-67-citrate scintigraphy, labeled leukocytes scintigraphy and PET was performed. Main findings of the literature were reported.

Results: Bone scintigraphy is a sensitive and widely available nuclear medicine technique, but it is characterized by low specificity. Gallium-67-citrate scintigraphy is often used as a complement to bone scintigraphy to enhance the specificity of the study and to detect extra-osseous sites of infection. Labeled leukocytes scintigraphy is not a useful method in the diagnosis of spondylodiscitis. Fluorine-18-fluorodeoxyglucose positron emission tomography is a sensitive method and could potentially be useful in the diagnosis of spondylodiscitis and in the evaluation of treatment response. Nevertheless, scientific literature about this topic is still limited.

Conclusions: Overall, nuclear medicine procedures play a useful role in the diagnosis of spondylodiscitis identifying functional abnormalities which precede morphological changes. Therefore, nuclear medicine procedures may complement or integrate morphological imaging findings in patients with suspected spondylodiscitis.

Key words: Nuclear medicine, Spondylodiscitis, Scintigraphy, Positron Emission Tomography.

Introduction

The diagnosis of spondylodiscitis (SP) can be difficult, because the patient's history, subjective symptoms and physical findings are often inconclusive, particularly in the early stages\(^1,2\). Nuclear medicine procedures, which identify pathophysiologic reactions preceding morphological changes, can play a useful role in the diagnosis of SP; several studies have investigated about the utility of nuclear medicine techniques with single photon emission tomography (SPET) and positron emission tomography (PET) tracers in the early diagnosis, staging and post-treatment evaluation in patients with SP\(^3\).
gate bone turnover\textsuperscript{4,6}. In SP, the radiopharmaceu-
tical uptake is centered about the disk space and
adjacent vertebral bodies and has a vertical orien-
tation. Early SP typically shows increased tracer
uptake on bone scintigraphy despite normal find-
ings on radiographs (Figure 1)\textsuperscript{5}.
Performing an hybrid tomographic single pho-
ton emission tomography/computed tomography
(SPECT/CT) acquisition provides a higher specific-
ity than planar scans; in fact, the improved
anatomical localization of sites of abnormal ra-
diopharmaceutical uptake in different vertebral
components is useful to distinguish between dif-
ferent spinal diseases which follow certain pre-
dictable patterns\textsuperscript{7,8}.
Overall, bone scintigraphy with Technetium-
99m-diphosphonates is well known for its high
sensitivity, ranging from 80 to 95\%, much
greater than conventional x-ray in the early diag-
nosis of SP: in fact, alterations in local blood
supply and in bone turnover detected by bone
scan occur far before anatomical changes\textsuperscript{9-13}. Fur-
thermore, if antibiotic therapy is initiated in early
stage, radiological abnormalities could not be ap-
parent\textsuperscript{9-13}. Thanks to its high sensitivity, a normal
bone scintigraphy provides very reliable evi-
dence for the absence of bone inflammation; on
the contrary, an increased uptake in all phases is
suggestive. Besides, the scanning of the entire
body allows the detection of eventual clinically
silent infectious focuses, whether in the spine
and in other bone segments. Since an intact vas-
culature in the affected bone is needed to allow
an adequate accumulation of the radiopharma-
caceutical, false negative results may be the conse-
quency of inadequate blood supply (vasospasm,
thrombosis of vessels, oedema), lytic lesions
with loss of osseous tissue or subperiosteal ab-
scesses\textsuperscript{9-13}. Nevertheless, abnormalities seen on
bone scintigraphy do not reflect infection specifically,
hence specificity is low, especially in the
setting of previous vertebral surgery (e.g. pro-
thetic implants) or injuries\textsuperscript{9-13}.

**Scintigraphy with autologous radiolabeled leukocytes**
Leukocytes, and particularly neutrophils, sig-
nificantly accumulate in the site of infection to
take part in the inflammatory response against
the microbial agent. Therefore, scintigraphy with
autologous radiolabeled leukocytes is a potential-
ly useful diagnostic tool in patients with spine in-
fec tion. Leukocytes labeling is obtained with
Technetium-99m-hexamethylpropylene amine
oxime (\textsuperscript{99m}Tc-HMPAO) or Indium-111-oxine,
even if the latter method has become obsolete for
most indications because of poor image resolu-
tion\textsuperscript{14}. However, disregarding the biological risk
related to the manipulation of infected blood, the
physiological uptake of leukocytes by the
hematopoietically active bone marrow (which
can be found in the axial bone segments such as
the skull, clavicles, sternum, scapulae, ribs, ver-
tebrae and pelvis) is the major drawback which
reduces the sensitivity of this method in the diag-
nosis of SP\textsuperscript{15}. Palestro et al\textsuperscript{16} reported a low sen-
sitivity (39\%) of scintigraphy with labeled leuko-
cytes in patients with SP when increased verte-
bral labeled leukocytes uptake was considered,
while specificity was very high (98\%). Pho-
topenic lesions at scintigraphy with labeled
leukocytes are shown in about 50\% of patients
affected by SP, probably due to encapsulation of
the infected site and therefore reduced migration
of leukocytes\textsuperscript{16,17}; nevertheless, this pattern is
nonspecific for infection.

**Scintigraphy with Gallium-67-citrate**
Infectious foci usually show high concentra-
tions of Gallium-67-citrate. Several mechanisms
have been proposed: binding to transferrin result-
ing in deposit to the sites of increased vascular
membrane permeability; binding to lactoferrin, a
globular glycoprotein with antimicrobial activity,
produced by innate immunitary system and abundant in the site of infection; direct uptake by certain bacteria through siderophores. The major drawback of Gallium-67-citrate scintigraphy is that only a small amount of the injected dose is retained by the bone, whereas a great amount is retained by the liver, bone marrow and soft tissues at 48 h and the 25% is physiologically excreted through the urinary system and the colon within the first 24 h. Furthermore, poor image quality, high bowel uptake in the early images requiring delayed images (up to 48-72 h) to reduce intestinal activity, nonspecific tumor and nodal uptake and an unfavourable physical half-life reduce the diagnostic yield of this method. Nevertheless, chronic infections of the spine are correctly identified by Gallium-67-citrate scintigraphy (Figure 2). Moreover, Gallium-67-citrate scintigraphy should be performed regardless of the findings of a contemporaneous bone scan: in fact, it improves the sensitivity and the specificity of bone scan and detects soft tissue involvement especially if performed with SPECT/CT modality. Love et al. found that Gallium-67-citrate SPECT is more accurate than bone scintigraphy with Technetium-99m-diphosphonates (92% vs 71%), as sensitive as MRI (91%) and slightly more specific than MRI (92% vs 77%). These Authors suggested that Gallium-67-citrate SPECT should be considered as a reliable alternative to MRI in case of diagnostic uncertainty and/or unfeasibility. Unfortunately, as Lin et al. described, postoperative uptake of Gallium-67-citrate at the site of surgical incision should be considered. Therefore, foci of Gallium-67-citrate uptake in an immediately post-surgical setting must be critically regarded. Despite its own limitations, scintigraphy with Gallium-67-citrate is less subjected to the interference of bone remodeling than bone scintigraphy with Technetium-99m-diphosphonates, being therefore more sensitive than bone scan in the follow-up evaluation of SP and in monitoring treatment response.

Role of PET in patients with spondylodiscitis

Fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) plays an important role in the diagnosis, staging and monitoring of malignant tumors. Not only tumors but also infections show an increased uptake of FDG (a glucose analogue), due to the increased glucose metabolism in activated inflammatory cells such as leukocytes. Therefore, in the last years, the role of FDG-PET and PET/CT in infectious and inflammatory diseases, beside oncologic field, is growing. Nevertheless, to date, scientific literature about this nuclear medicine technique in the field of SP is limited.

FDG-PET is a very sensitive imaging procedure in the detection of SP (Figure 3). Compared to other nuclear medicine procedures, PET enables a rapid imaging with acceptable radiation dose and high spatial resolution. The sensitiv-
ity and specificity in detecting SP infection is very high if FDG-PET is used in addition to conventional tests and imaging. Furthermore, FDG-PET is recommended for distinguishing between common Modic change at radiological imaging and spinal infection. Gratz et al. reported that FDG-PET was superior to MRI, scintigraphy with Gallium-67-citrate and Technetium-99m-diphosphonates, especially in patients with low-grade spondylitis (as compared with MRI), adjacent soft tissue infections (as compared with scintigraphy with Gallium-67-citrate) and advanced bone degeneration (as compared with scintigraphy with Technetium-99m-diphosphonates).

It is possible to clearly differentiate between infections of vertebrae and adjacent soft tissue infections by using hybrid FDG-PET/CT. Furthermore, this modality is also capable of demonstrating the extent of the infection. This may be helpful in assessing the paravertebral abscess in SP. Hybrid PET/CT systems offer an excellent anatomic localization of the actual site of uptake, minimizing misinterpretation of localization from areas of arthritic bony disease and infection, such as demonstrating the uptake to be associated with an arthritic facet joint rather than with the vertebral body or interspace.

Furthermore, FDG-PET allows quantification of inflammatory activity: in fact, a decreased FDG uptake generally corresponds to a clinical improvement. Therefore, the quantification of inflammatory activity might be useful for treatment monitoring. Kim et al. reported that FDG-PET is useful for the discrimination between residual and non-residual spine infections after therapy.
Overall, FDG-PET is a very promising alternative to conventional nuclear medicine procedures, appearing to be superior in the detection of spinal infections and in the differentiation of degenerative from infectious end-plate abnormalities. The advantages of PET are obvious: the study is sensitive, is completed in a single session, and image resolution is superior to that obtained with conventional nuclear medicine procedures. As with Gallium-67 scintigraphy, however, specificity remains an issue. While FDG uptake in uninfected fractures may normalize more rapidly than gallium or diphosphonate uptake, differentiating infection from tumor may still be problematic. Moreover, inflammatory reactions incited by spinal implants also may adversely affect specificity. Nevertheless, there is an expanding body of evidence that supports the use of FDG-PET and PET/CT for diagnosing spinal infections, especially in patients with MRI contraindications and in the post-operative spine. In fact, morphological imaging techniques rely on structural changes to make diagnosis but when normal anatomy is distorted by post-surgical changes or scarring or in the presence of implants, these techniques are less reliable. Functional imaging studies are performed to improve diagnostic accuracy showing high negative predictive value, especially in these cases. Nevertheless, several examinations are required to strengthen any diagnosis of SP; the use of FDG-PET alone is not recommended.

Recently, Nanni et al. reported promising results of Gallium-68-citrate PET/CT in a population of patients with suspected bone infections, including nine patients with SP. Although preliminary, these data confirm a possible role for Gallium-68-citrate as a PET tracer in the diagnosis of SP, especially in consideration of its favorable characteristics.

In conclusion, more studies are necessary to validate the usefulness of PET imaging with different tracers (FDG or Gallium-68) in patients with SP.

**Conclusions**

Overall, nuclear medicine procedures play a useful role in the diagnosis of spondylodiscitis identifying functional abnormalities which precede morphological changes. Therefore, nuclear medicine procedures may complement or integrate morphological imaging findings in patients with suspected SP.
The role of nuclear medicine in the diagnosis of spondylodiscitis