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The Spine Journal ■■ (2017) ■■–■■

THE SPINE JOURNAL

Clinical Study

Validation of topographic hybrid single-photon emission computerized tomography with computerized tomography scan in patients with and without nonspecific chronic low back pain. A prospective comparative study

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Received 13 December 2016; revised 10 March 2017; accepted 2 May 2017

Abstract

BACKGROUND CONTEXT: The evidence for the treatment for nonspecific chronic low back pain (ns CLBP) is very weak. Besides the complexity of the pain experience, a good biological marker or tool enabling identification of a pain generator is lacking. Hybrid imaging, combining single-photon emission computerized tomography (SPECT) with computerized tomography (CT) scan, has been proposed as useful in the diagnostic workup of patients with CLBP.

PURPOSE: To evaluate the sensitivity of SPECT-CT in patients with ns CLBP (Group I) as compared with patients without CLBP (Group II).

STUDY DESIGN: A prospective comparative study.

PATIENT SAMPLE: Two hundred patients were enrolled: 96 in Group I and 104 in Group II.

OUTCOME MEASURES: Only the physiological measurement of the incidence of hot spots was performed.

The hot spots were rated as follows: 0=normal; 1=slightly colored (no hot spot on whole-body bone scan); and 2=clear hot spot (can be identified on the whole-body bone scan and confirmed on SPECT). To analyze the interobserver agreement when using this scoring system, a second independent reading was performed for 50 randomly chosen records.

METHODS: Two hundred patients divided into two groups were referred to the department of Medical and Molecular Imaging for a topographic SPECT-CT.

The first group consisted of patients with ns CLBP, diagnosed by a neurosurgeon. The control group consisted of patients referred for SPECT-CT for non-spinal conditions. Hot spots were assessed for all patients.

A second independent reading, blinded for the results of the first reader, was performed on 25 randomly selected patients in each group.

This study was investigator initiated, and no funding was received. None of the authors or their proxies have a potential conflict of interest.

RESULTS: The odds of finding a normal image in the control group are 2.05 times higher than in Group I. The sensitivity score equals 2.37, meaning that the probability of detecting a hot spot (levels 1 or 2) is more than two times higher in Group I. When focusing on level 2 hot spots only, this score rises to 7.02, indicative of a high sensitivity.

FDA device/drug status: Not applicable.

Author disclosures: ***EVdK:*** Nothing to disclose. ***GV:*** Nothing to disclose. ***A-SVdK:*** Nothing to disclose. ***KM:*** Nothing to disclose. ***JVG:*** Nothing to disclose.

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http://dx.doi.org/10.1016/j.spinee.2017.05.007

CONCLUSIONS: Single-photon emission computerized tomography with computerized tomography might have potential in the diagnostic workup of patients with ns CLBP, owing to its higher sensitivity when compared with other advanced medical imaging modalities.

Keywords: Altered bone metabolism; Diagnosis; Facet osteoarthritis; Inflammation of lumbar disc; Magnetic resonance imaging (MRI); Nonspecific low back pain; Outpatient clinic; Pain generator; SPECT-CT; Vertebral end plates

Introduction

Today, in the Western world, low back pain (LBP) is the leading cause of disability [1]. Low back pain is ranked as the second most common symptomatic reason for physician office visits in the United States [2]. Chronic low back pain (CLBP; defined as daily LBP for at least 3 months) with an intensity of >5 on a 10-point pain scale, has 9.9%-point prevalence, and 51.2% lifetime prevalence [3].

Yet there is rather weak or no evidence for effective treatment options, which is mainly owing to the lack of a diagnostic tool allowing the identification of a pain generator. In medical literature, CLBP is defined as specific when due to a tumor, trauma, infection, or inflammation. In more than 85% of patients with CLBP, however, these conditions cannot be found and, therefore, their CLBP is defined as nonspecific (ns CLBP) [1,4]. The currently available evidence regarding the pathologic and clinical significance of magnetic resonance (MR), computerized tomography (CT) scan, and X-ray findings in patients with ns CLBP remains very weak, except for Modic type 1 changes, active Schmorl nodules at the vertebral end plates, and mechanical instability on X-rays [5–7]. In these cases, the correlation with CLBP seems to be very high [8,9]. Nevertheless, today, these conditions are still defined as ns CLBP.

The lack of correlation between advanced medical imaging modalities and most conditions of ns CLBP justifies the search for more clinical subtypes of ns CLBP, as well as our attempts to validate new diagnostic tools.

^{99m}Tc methylene diphosphonate bone scintigraphy is a highly sensitive method for detecting bone disease and can enable detection of altered bone metabolism and increased regional blood flow as occurs in some stages of osteoarthritis [10]. The use of hybrid imaging, combining single-photon emission computerized tomography (SPECT) with CT scan, has been proposed as a useful adjunct in the diagnostic workup of patients with CLBP. The development of multimodality SPECT-CT has allowed the coupling of the previously reported high sensitivity of bone scintigraphy with the anatomical specificity of the CT scan. Because of its superior resolution, a correct interpretation of osteoarticular structures becomes possible, even on low-dose (topographic) CT scan [11]. High-dose (diagnostic) CT scan offers additional diagnostic values, such as the identification of lumbar disc herniation.

In this prospective comparative study, we evaluate the sensitivity of SPECT-CT in patients with ns CLBP as compared with patients without CLBP. We assume that there is a significant difference in the number of hot spots on SPECT-CT between the two groups and that, if we consider only clear hot spots as indicative of altered bone metabolism, the odds of finding these lesions in the control group is significantly lower than in the symptomatic group.

Materials and methods

The local ethical committee approved the protocol (EC13022). The study was registered under the number ISRCTN52513588.

We prospectively studied 200 patients divided into two groups.

The first group consisted of patients with ns CLBP, defined as daily LBP (visual analog scale [VAS] >5/10) for at least 3 consecutive months, no specific pain generator, and no neurologic signs or symptoms. Patients were recruited in an outpatient spine clinic and included if on magnetic resonance imaging (MRI); specific causes of CLBP such as tumor, trauma, inflammation, and infection of the lumbar spine were excluded; and if after clinical examination by a neurosurgeon (EVdK), patients had no neurologic symptoms or signs. Patients with a specific LBP (due to inflammation, infection, trauma, tumor) or with neurologic signs and symptoms were excluded from this analysis [1,12]. When these patients presented for the SPECT-CT, they were asked if they still had LBP; if this was not the case, they were excluded from the study.

The control group consisted of patients referred for SPECT-CT for non-spinal conditions. They were not seen by a neurosurgeon or any other physician for LBP problems and they had no recent medical imaging of their lumbar spine. Upon presentation to the department of Medical and Molecular Imaging, they were questioned about LBP. In case they had experienced LBP during the 3-month period before the SPECT-CT imaging, they were excluded from the study. Apart from the investigation of the anatomical structures they were referred for, they received an additional topographic SPECT-CT of the lumbar spine.

The exclusion criteria for both groups were as follows: pregnancy, presence or history of malignancy, recent spine trauma, previous lumbar spine surgery, a specific LBP, or neurologic symptoms and signs.

All patients received a full explanation about the study and signed the informed consent.

SPECT-CT imaging

Imaging for both patient groups was performed on a dual-head, hybrid SPECT-CT gamma camera (GE Discovery NM/CT 670, GE Healthcare; Barrington, IL, USA) with a low-energy high-resolution collimator. Whole-body scintigraphy and SPECT-CT imaging were performed two to four hours after intravenous administration of 700 MBq ^{99m}Tc-HDP.

Single-photon emission computerized tomography images were acquired in a 60-step (20 s/stop), 360° noncircular orbit and reconstructed in a 128×128 matrix using a three-dimensional ordered-subsets expectation maximization algorithm. Data were reconstructed by iterative reconstruction using evolution with four subsets and eight iterations, using a gaussian filter.

A CT transmission scan was acquired after the SPECT study. The CT parameters used were 120 kVp and automated exposure control for both patient groups. Reconstruction was performed in a 512×512 matrix at a slice thickness of 5 mm. The CT was co-registered with the SPECT using the nuclear medicine workstation. Computerized tomography attenuation correction was applied to SPECT images. Single-photon emission computerized tomography (SPECT) with computerized tomography studies were viewed in the coronal, axial, and sagittal planes and in three-dimensional mode. Computed tomography was performed with ultra low dose to anatomically localize any hot spots detected on SPECT. Computerized tomography images therefore were not of diagnostic quality and not evaluated for both patient groups.

The reading of the SPECT image of each patient was done by a nuclear medicine physician, blinded to the patient's basic characteristics and consisted of a visual interpretation, without any quantification, because no valid quantification method has been published yet. The presence of hot spots was recorded for the lumbar end plates, the lumbar facet joints, and for the sacroiliac joints. The reading and interpretation of the hot spots was done using the protocol below.

Reading and interpretation of the images with three levels:

0=normal (no increased bone uptake neither on whole body bone scan nor on SPECT-CT images)
1=slightly colored (moderate bone uptake) (no hot spot on the whole-body bone scan, only on the SPECT-CT images) (Figs. 1 and 2)
2=clear hot spot (clearly identified on whole-body bone scan and confirmed on SPECT) (Figs. 1 and 2)

To analyze the interobserver agreement when using this scoring system, a second independent reading was performed. A nuclear medicine physician, blinded for the results of the first reader, interpreted the same SPECT-CT images in a limited series; the data of 50 random patients were retrieved and analyzed.

Although the VAS score was used as an inclusion criterion of patients with ns CLBP, afterward, no correlation was made between VAS score and hot spots.

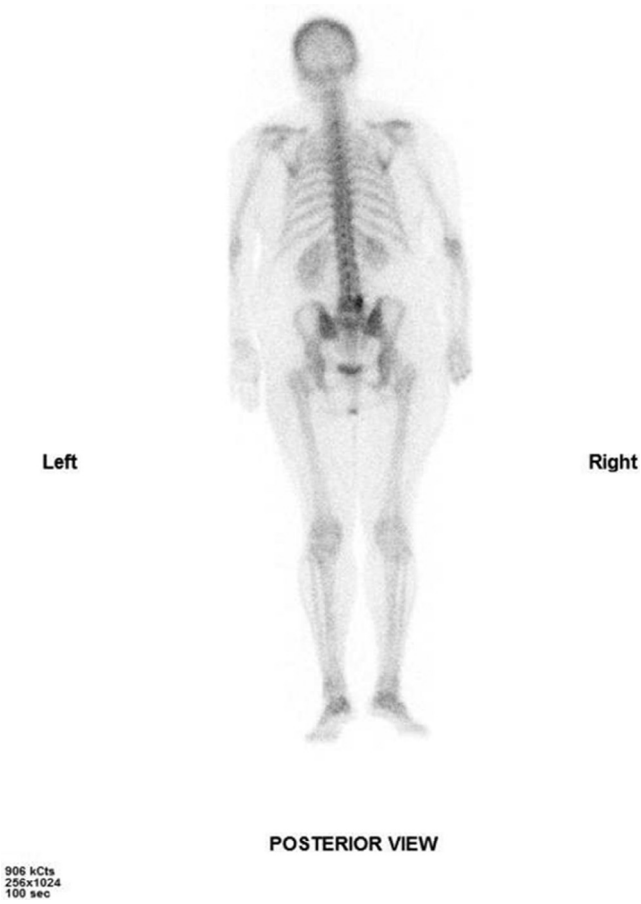

Fig. 1. Whole-body imaging bone scintigraphy clearly indicating a hot spot at the lower lumbar level on the right. When a hot spot is seen on this image, we classify it as level 2. To identify the exact anatomical structure that is affected, the topographic computerized tomography (CT) scan image is used (Fig. 2).

Statistics

Demographic data were analyzed using the chi-square test for cross tables and the independent groups *t* test [13] (SPSS; Released 2013. IBM SPSS Statistics for Windows, Version 22.0; IBM Corp, Armonk, NY, USA).

One-sided percentage tests were used to detect differences in the % of hot spots (all hot spots together and level 2 hot spots separately) between the two groups (Statistica 7, Released 2004, Statsoft Inc, Tulsa, OK, USA) [14].

Interobserver variability was analyzed as % agreement, kappa coefficient (SPSS) [15], and the Spearman rho correlation coefficient (SPSS) [16].

Results

Two hundred patients were enrolled between August 2013 and February 2015, 96 (of which 46.6% were male) in the ns CLBP group and 104 (of which 44.68% were male) in the control group. The mean age was 50.17 and 47.07 years, respectively. Three patients were excluded from analysis, one in the control group because of previous back surgery and

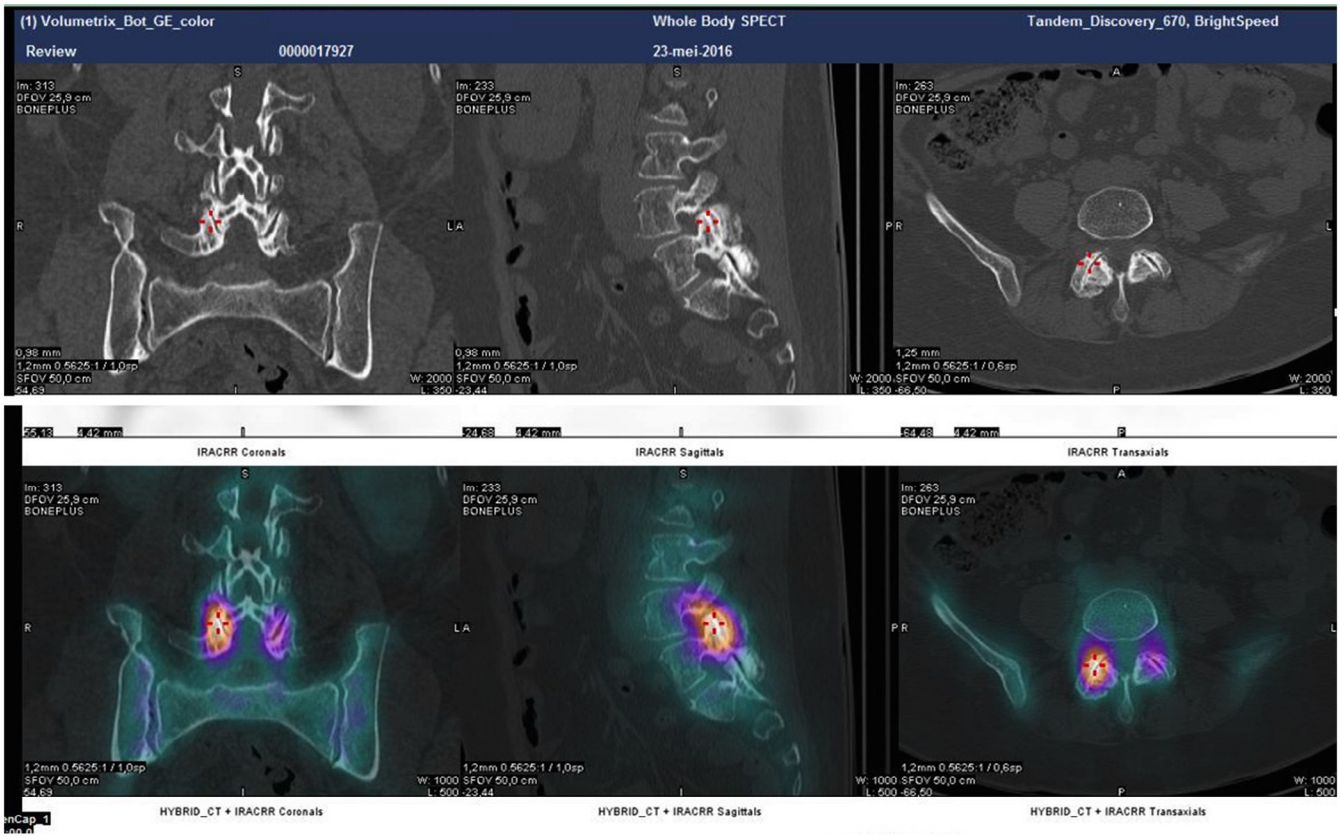

Fig. 2. (Top) The topographic computerized tomography (CT) scan images, taken in the three anatomical planes, can be fused with the single-photon emission computerized tomography (SPECT) images to show the exact anatomical localization of the hot spot. This topographic CT image is not used to make a diagnosis on anatomical findings. (Bottom) The fusion images between the SPECT and the CT scan findings, confirming the hot spot detected in Fig. 1 as altered bone metabolism at the right facet joint L4–L5. This lesion is classified as a level 2 hot spot. At the same level, to the left, there is a slightly colored spot at the facet joints, not seen on the whole-body imaging, which is therefore classified as level 1. All other anatomical locations analyzed (facet joints, end plates, and both the sacroiliac joints [SIJ]) are classified as "zero" for this patient.

two in the CLBP group also because of previous back surgery. Both groups matched regarding age (t=−1.570, df=195, and p=.118.) and gender (chi-square=0.077, df=1, and p=.782).

The Table presents the distribution of the observed hot spots.

Table
Observation of hot spot types 1 and 2 and hot spot type 1 alone

	CLBP, n=94	CLBP %	Control, n=103	Control %	p
Normal	29	30.85	65	63.22	.000
Facets 1 and 2	40	42.55	23	22.33	.013
Facet 2	14	14.89	5	4.85	.09
End plates 1 and 2	45	47.87	19	18.45	.000
End plate 2	15	15.96	0	0	.000
SIJ 1 and 2	5	5.32	0	0	.0094
SIJ 2	3	3.19	0	0	.0346

CLBP, chronic low back pain; SIJ, sacroiliac joints.
Facets 1 and 2: hot spot levels 1 and 2 at the facet joints.
Facet 2: hot spot level 2 at the facet joints.
End plates 1 and 2: hot spot levels 1 and 2 at the vertebral end plates.
End plates 2: hot spot level 2 at the vertebral end plates.
SIJ 1 and 2: hot spot levels 1 and 2 at the sacroiliac joints.
SIJ 2: hot spot level 2 at the sacroiliac joints.

There is a significant difference between the two groups in incidence of normal images and hot spots at the different vertebral structures. In the control group, 5 of 103 patients (4.85%) had level 2 hot spots at one or more lumbar facet joints. No level 2 hot spots were noticed at the vertebral end plates or at the sacroiliac joints in this group. The difference between the two groups for level 2 hot spots in all locations is highly significant, indicating a high sensitivity (Table).

The odds of finding a normal image in the control group are 2.05 times higher than in the ns CLBP group. By adding up information from the three spine locations, this sensitivity score equals 2.37, meaning that the probability of seeing a hot spot (levels 1 or 2) is more than two times higher in the ns CLBP group. Focusing on level 2 hot spots only, this score rises to 7.02.

Interobserver reliability

An equally qualified nuclear medicine physician assessed the images from 50 randomly chosen persons a second time. The data were analyzed with three parameters: % agree-

ment, kappa coefficient, and the Spearman rho correlation coefficient.

Global analysis shows 96.73% agreement. Kappa yields 0.70, indicating a much higher overlap than what we expect to see by mere chance, and the correlation equals 0.753. Comparison of the number of hot spots of the three levels in the ns CLBP group (N=23) and the control group (N=27) shows a comparable distribution for the defined region with the global group. The agreement level is 95.06% in the patient group and 98.15% in the control group. Kappa equals 0.692 in the CLBP group and 0.709 in the control group. Spearman rho equals 0.770 in the CLBP patient ratings and 0.711 in the control group. As such, this scoring system can be considered as reliable.

Discussion

The incidence of hot spots on topographic SPECT-CT of the lumbar spine is significantly higher in patients with ns CLBP as compared with a control group. The highest incidence of hot spots is recorded at the vertebral end plates. When considering only the level 2 hot spots, the odds of finding a normal image in the control group are 7.02 times higher than in the ns CLBP group, indicating a high sensitivity. As such, our assumption can be confirmed.

Others have reported the high incidence of hot spots at the lumbar spine in patients with CLBP. In 2011, Carstensen et al. [17] were impressed by a hybrid SPECT-CT of the lumbar spine of one of their patients, showing active bone metabolism in the right L3–L4 facet joint, with minimal signs of facet degeneration on the CT scan images, whereas a segment demonstrating more gross degenerative changes on CT scan images was more quiescent with only mild tracer uptake on the SPECT images. They argued that SPECT-CT for anatomical and functional assessment of CLBP might open promising opportunities for multidisciplinary clinical assessment. Several others tried, in retrospective non-comparative studies, to assess the value of SPECT-CT in patients with CLBP [11,18–21]. They identified "potential pain generators" in up to 86% of SPECT-CT scans of the lumbar spine [6]. In another retrospective analysis of 534 patients with "spinal pain," 91.1% had at least one hot spot [18].

A recently published randomized controlled trial stated that SPECT-CT had only moderate sensitivity (0.57) and specificity (0.77) and should not be recommended as first-line diagnostic tool before diagnostic infiltrations [22]. This is a study on a small (29) patient sample with suspected facet joint pain who received a SPECT-CT and afterward diagnostic blocks of the medial branch of the dorsal ramus. The SPECT-CT results were not used as guidance for the location of the diagnostic blocks.

To the best of our knowledge, we report the first prospective, comparative study on SPECT-CT findings in both patients with ns CLBP and a control group. The asymptomatic control group exhibited a Grade 1 positive SPECT in 37 patients (35.9%). Only 4.85% showed Grade 2 positive SPECT. This finding contrasts with the reports on other types of medical imaging, such as plain radiography, CT scan, or MRI. Abnormal morphological findings of the lumbar structures (in particular, bones, joints, and discs) on anatomical imaging modalities have been shown to exist equally in asymptomatic individuals [23]. Plain radiography therefore is not recommended as a routine diagnostic tool for patients with ns CLBP [24]. Some studies found a very poor correlation between facet joint degeneration identified on CT scan and LBP in a community-based setting [25]. In 1994, Jensen et al. [5] published their findings of multiple bulging and protruding lumbar discs, detected on MRI in asymptomatic patients. Recently, however, there is some indication that, in ns CLBP, on MR, Modic type 1 changes and active Schmorl nodules are correlated with LBP [8,9]. These MR findings have even been correlated with hot spots on SPECT-CT images [26,27]. The characteristics of these entities are not exclusively based on anatomical changes, but one can detect functional ones, seen as bone edema of the end plates. Because most imaging modalities are based on morphological characteristics, however, they are in most cases unable to differentiate between incidental and relevant changes.

Single-photon emission computerized tomography with computerized tomography is a functional molecular imaging modality that could potentially be used, additionally to morphological diagnostic tools, to differentiate incidental from clinically relevant findings. However, today, it is still hard, if not impossible, to measure the specificity of the reported hot spots, because we cannot clinically confirm them as the real pain generators.

Although the sensitivity of hot spots on SPECT-CT imaging in patients with ns CLBP is high, we noted no hot spots in 30.85% of these patients and we recorded a level 2 hot spot in 5% of the asymptomatic study population. To understand these results, one must realize what the different pathophysiological mechanisms of CLBP are and what SPECT-CT measures.

Single-photon emission computerized tomography itself is a tomographic scintigraphic technique in which a computer-generated image of local radioactive tracer distribution in tissues is produced through the detection of single-photon emission from the intravenously injected -diphosphonates. These ^{99m}Tc-diphosphonates are incorporated into every osteoblastic activity, but also show up in regions with even slightly elevated blood flow [28,29]. As SPECT-CT measures radiation, it is obvious that hot spots will be observed wherever such osteoblastic activity or increased regional blood flow is present. The osteoblastic activity can be the result of osteoarthritis, common in synovial joints, or at the level of the subchondral bone of the vertebral end plates in case of disc degeneration [30]. It is characterized by focal areas of damage to the articular cartilage, associated with increased regional blood flow and new bone formation at the joint margins (osteophytosis). In the acute phase of inflammation, this altered bone metabolism will be associated with pain. But in the chronic phase (ie, more osteophyte

formation at the load-bearing areas of the joint), bone activity may proceed without pain. This explains the hot spots in asymptomatic patients. As such, a positive finding on SPECT-CT imaging in a patient with CLBP does not mean that the affected anatomical structure is the responsible pain generator. On the other hand, it is very likely, because we rarely see these level 2 hot spots (5%) in asymptomatic people. This finding is very different from the ones reported on CT scan and MRI [1,4,5,24].

To understand why no hot spots are detected in 30.85% of symptomatic patients, we should understand the pathophysiology of CLBP [31,32]. Intervertebral discs are considered to be one of the main pain foci in these patients [33]. Hot spots can be seen at the end plates of the vertebral bodies, indicating subchondral bone alteration due to disc degeneration. This condition must not always be considered as pathological, because it has been reported in many cases as a silent phenomenon of degeneration [21]. A diseased disc can, however, cause pain before the cascade of altered bone metabolism starts [32]. In this condition, the patient may suffer from ns CLBP, with a normal SPECT-CT image.

The lumbar facet joints are true synovial joints, where osteoarthritis, when aging, is a common but not a pathological phenomenon [34]. A diagnostic tool that indicates the facet joint as an isolated pain generator is not available yet. Pain can be provoked by stretching of the joint capsule, or by a synovitis. Both can be detected on SPECT-CT imaging in case the pathology is accompanied with altered regional blood flow. If this is not (yet) the case, the patient may suffer from ns CLBP, with a normal SPECT-CT image. As such, pain originating from a facet joint does not necessarily result in a hot spot on SPECT-CT.

It is obvious that pain originating from ligaments and muscles, if this pain mechanism is not responsible for an increased regional blood flow (yet), cannot be detected on SPECT-CT.

Further, the nervous system response and modulation mechanisms in response to long-standing pain, such as peripheral and central sensitization, as well as psychological or personality and social factors influencing pain experiences, are beyond the detection possibilities of this advanced functional medical imaging modality.

This study has some drawbacks. We decided not to use the information obtained by the CT scan for the following two reasons. First, it is well known that the correlation between imaging findings on CT scan and ns CLBP is poor [1]. Second, in the control group, we performed a CT scan of the lumbar spine in patients without CLBP. Therefore, the radiation dose was lowered to a level that was sufficient to add topographic information to the SPECT, enough to identify the anatomic osteoarticular structures, but insufficient to make a reliable CT diagnosis.

The interpretation of the images is another topic of debate. In contrast to PET imaging, the quantification of lesions by means of a standard uptake value is not (yet) feasible for SPECT. As such, the interpretation of the images is performed by visual analysis and hence subjective. Although the creation of three levels of uptake, as we did, is artificial, it reflects the way images are interpreted and reported in a clinical practice today. In this study, we performed, however, an interobserver analysis, which turned out to be good. Therefore, this quantification on a visual analysis can be promoted for other scientific purposes.

While analyzing the results of this study, one should be very careful with the interpretation and implementation of our results. In this study, SPECT-CT of the lumbar spine, when evaluating patients with ns CLBP, indicates in most cases (71%) an anatomical structure with altered bone metabolism. This hot spot, however, is not per se the main pain generator.

However, combined with a good interobserver variability, these results suggest that SPECT-CT has potential in the diagnostic workup of patients with ns CLBP, because the sensitivity is better than the one of other advanced medical imaging techniques. Further evaluation of this functional imaging modality, particularly in therapeutic trials, is needed to define its place and role in the workup of CLBP and its possible impact on patient management and outcome.

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