

# Somatostatin receptor scintigraphy in sarcoidosis: relation to selected clinical and laboratory markers

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## KEY WORDS

biomarkers, exhaled breath condensate, sarcoidosis, somatostatin receptor scintigraphy, 8-isoprostane

## ABSTRACT

**INTRODUCTION** Discriminating between active and inactive sarcoidosis may be problematic in every-day clinical practice. There are numerous biochemical markers used in the diagnosis and monitoring of sarcoidosis. Somatostatin receptor (SR) scintigraphy with the use of <sup>99m</sup>Tc-octreotide may be used to estimate disease activity.

**OBJECTIVES** The aim of the paper was to assess the value of traditional biomarkers (serum angiotensin-converting enzyme [SACE], C-reactive protein, markers of calcium metabolism, bronchoalveolar lavage fluid [BALF] lymphocytes) and a novel biomarker, 8-isoprostane (8-IP) in exhaled breath condensate (EBC), in the assessment of sarcoidosis activity in relation to somatostatin receptor scintigraphy.

**PATIENTS AND METHODS** The study included 32 patients with sarcoidosis. Scintigraphy was performed using somatostatin analogue, <sup>99m</sup>Tc-HYNIC-TOC; planar and SPECT/CT images were recorded. The study group was divided into a subgroup with positive radiotracer uptake ( $n = 20$ ) and without a visible uptake ( $n = 12$ ). 8-IP levels were measured in EBC by an immunoenzymatic assay.

**RESULTS** We observed a significantly higher EBC 8-IP levels in the subgroup with positive uptake compared with those with negative uptake ( $19.1 \pm 19.8$  vs.  $5.4 \pm 3.5$  pg/ml,  $P = 0.02$ ). The levels of SACE and the percentage of BALF lymphocytes were also nonsignificantly elevated. In the group of patients with positive scintigraphy results, a positive correlation was observed between the uptake ratio and SACE ( $r = 0.44$ ,  $P = 0.041$ ).

**CONCLUSIONS** The results indicate low value of biochemical markers in the assessment of disease activity. SR scintigraphy may have practical usefulness in the monitoring of sarcoidosis.

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**INTRODUCTION** Sarcoidosis is a chronic granulomatous inflammatory disease of unknown origin. In the majority of cases, the disease disappears spontaneously without sequelae, but chronic and progressive course is also common. The most serious complication of sarcoidosis is lung fibrosis, which may lead to respiratory insufficiency and is the most frequent cause of death.<sup>1</sup> Only patients with active inflammation may benefit from treatment; therefore, differentiation between active inflammation and inactive changes may be crucial.

The early reports on gallium (<sup>67</sup>Ga) scintigraphy revealed a good correlation with disease activity, its clinical usefulness in detecting extrapulmonary locations, and the most convenient approach for biopsy. High activity of radiotracer in the area of hilar and right paratracheal lymph nodes (lambda pattern) is considered highly specific for sarcoidosis.<sup>2</sup> Somatostatin receptor (SR) scintigraphy is based on the uptake of <sup>111</sup>In- or <sup>99m</sup>Tc-labeled octreotide derivatives, such as <sup>99m</sup>Tc-octreotide, or other somatostatin analogues, by somatostatin subtype 2 receptors.<sup>3</sup> This method is effective

in the diagnosis of neuroendocrine tumors,<sup>3</sup> solitary lung nodules,<sup>4</sup> and evaluation of patients with sarcoidosis, due to the presence of somatostatin receptors on the surface of epithelioid and giant cells, which form the sarcoid granuloma.<sup>5</sup> Lebtahi et al.<sup>5</sup> showed that scintigraphy with somatostatin analogues was superior to <sup>67</sup>Ga scintigraphy in the evaluation of patients with sarcoidosis, especially in the estimation of extrapulmonary involvement and in patients treated with corticosteroids.

Several laboratory markers are used for the estimation of sarcoidosis activity, such as serum angiotensin-converting enzyme (SACE), C-reactive protein (CRP), and indices of calcium metabolism. Unfortunately, the sensitivity of these markers is low. It has been estimated that the levels of SACE, serum calcium (S-Ca<sup>2+</sup>) and 24-hour urinary Ca<sup>2+</sup> (U-Ca<sup>2+</sup>) loss were elevated in 60%, 11%, and 40% of the patients with active disease, respectively.<sup>6,7</sup> Moreover, all these markers may be elevated in diseases other than sarcoidosis.<sup>8,9</sup> Severe impairment of calcium metabolism has adverse prognostic value.<sup>1,9</sup> According to a number of researchers, the increased percentage of bronchoalveolar lavage fluid (BALF) lymphocytes may be found in up to 90% of patients with newly-diagnosed sarcoidosis,<sup>10</sup> but neither the increased percentage of BALF lymphocytes nor increased CD4 to CD8 ratio is associated with a worse long-term prognosis.<sup>11,12</sup> A score of interstitial lung diseases different from sarcoidosis may be accompanied by lymphocytic alveolitis.<sup>10</sup>

8-isoprostane (8-IP) is a product of nonenzymatic peroxidation of arachidonic acid. It may be measured in exhaled breath condensate (EBC) and was proposed as a novel inflammatory marker in asthma and chronic obstructive pulmonary disease.<sup>13,14</sup> Its levels were elevated in the EBC of patients with sarcoidosis,<sup>15,16</sup> and were strongly correlated with the BALF levels of this marker.<sup>16</sup> Some data show a better prognosis in patients with low initial 8-IP levels in exhaled breath.<sup>17</sup> 8-IP levels did not correlate with BALF lymphocytes,<sup>16,17</sup> but correlated with SACE levels.<sup>15</sup> The potential usefulness of 8-IP in sarcoidosis is yet undefined.

The main purpose of this study was to verify the value of traditional laboratory markers (SACE, CRP, S-Ca<sup>2+</sup> level, and 24-hour U-Ca<sup>2+</sup> loss, BALF lymphocytes) and a novel potential biomarker, EBC 8-IP, vs. SR scintigraphy results.

**PATIENTS AND METHODS** **Study group** The study group consisted of 32 nonsmoking patients (15 women), aged 25–71 years (mean ± standard deviation = 43 ± 12). Sarcoidosis was diagnosed based on clinical and radiological criteria and confirmed by biopsy.<sup>1</sup> All patients signed an individual consent. The study was approved by the Ethics Committee at Medical University of Lodz (RNN/99/08/KE).

Patients were divided according to chest X-ray results to stage 0 (normal, n = 4), stage I (enlarged

hilar lymph nodes, n = 15), stage II (lymph node and parenchymal changes, n = 8), stage III (parenchymal changes, but no evidence of fibrosis, n = 3), and stage IV (fibrosis, n = 2). A history of Löfgren syndrome was reported by 16 patients, in 2 of them descending erythema nodosum was present at the time of investigation. Nine patients (25%) were on prednisone treatment (5–20 mg/day).

**Somatostatin receptor scintigraphy** Whole-body planar imaging in the anterior and posterior positions was performed with a dual-head hybrid gamma camera, Infinia Hawkeye GE, 2 hours after intravenous administration of 740 MBq of <sup>99m</sup>Tc-HYNIC-TOC (300-second acquisition time per projection). SPECT/CT imaging of the mediastinum was performed (matrix 128 × 128; multiple views over 360° at a 30-second acquisition time per projection with an angular step of 3°), and were reconstructed by iterative ordered subset expectation maximization method (2 iterations, 10 substeps, postfilter Hann 0,9) with a scatter and attenuation correction based on computed tomography (CT) attenuation maps. Processing of CT transmission scans and nuclear medicine data was performed on dedicated workstation (Xeleris, GE Healthcare). Scintigraphic images were evaluated by 2 independent nuclear medicine specialists and by consensus qualified as 0 (no visible regions of uptake) or 1 (visible regions of increased radiopharmaceutical uptake). For regions of visible uptake, semiquantitative measures of uptake were calculated as the ratio of counts (region/background). Patients with grade 0 (n = 12) were further treated as a negative control group. In all patients, it was consistent with the clinical diagnosis of inactive sarcoidosis.

**Bronchoscopy with bronchoalveolar lavage fluid collection** Bronchoscopy with BALF collection was performed with a flexible bronchoscope (Pentax, Japan) according to the British Thoracic Society Guidelines.<sup>18</sup> BALF was collected from the medial lobe by instillation and subsequent withdrawal of 4 × 50 ml of 0.9% NaCl. Cytospin slides were prepared and stained by the May-Grünwald-Giemsa stain. Lymphocytes and other cells were calculated with the use of light microscopy and presented as the percentage of all cells.

**Lung function tests** Spirometry was performed according to the European Respiratory Society/American Thoracic Society (ERS/ATS) standards,<sup>19</sup> using the Jaeger spirometer (Germany). The forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV<sub>1</sub>) were measured, and the Tiffeneau index (FEV<sub>1</sub>/FVC) was calculated. Lung diffusion capacity for carbon monoxide was measured on Lungtest 1000 SB (MES, Poland) with a single breath method, according to the ERS/ATS standards,<sup>20</sup> and corrected for hemoglobin. All data (except the Tiffeneau index)

**TABLE 1** Radiological and clinical data in the subgroups with grade 0 (negative radiotracer uptake) and 1 (positive radiotracer uptake)

Parameter	Grade 0 n = 12	Grade 1 n = 20	P
age, y, mean $\pm$ SD	41.0 $\pm$ 10.0	44.0 $\pm$ 12.5	0.54
sex, female/male	6/6	9/11	0.78
X-ray stage 0/I/II/III/IV, n	3/4/3/1/1	1/11/5/2/1	0.51
HRCT scoring (total), mean $\pm$ SD	4.83 $\pm$ 2.95	5.10 $\pm$ 3.40	0.81
HRCT scoring (parenchymal), mean $\pm$ SD	3.00 $\pm$ 2.49	2.90 $\pm$ 2.65	0.92
Löfgren syndrome	3 – past 0 – present	9 – past 2 – present	0.16
extrapulmonary locations (all past)	eye – 1	skin (other than EN) – 1 Heerfordt syndrome – 1	0.88
respiratory symptoms (cough, shortness of breath), n (%)	3 (27)	5 (25)	0.89
general signs and symptoms (malaise, weight loss, headache, arthralgia, myalgia), n (%)	3 (27)	5 (25)	0.89
number of treated patients	2	7	0.15

Abbreviations: EN – erythema nodosum, HRCT – high-resolution computed tomography, SD – standard deviation

were presented as the percentage of the predicted value.<sup>19,20</sup>

**Exhaled breath condensate collection** EBC was collected using a condensing device (Ecoscreen, Jaeger, Germany), and following the available recommendations.<sup>21</sup> Patients were asked to breathe out spontaneously for 10 minutes, with respiratory rate from 15 to 20 breaths/min. Samples were stored at  $-80^{\circ}\text{C}$  until measurements.

**8-isoprostane** The levels of 8-IP were measured by a specific enzyme immunoassay (EIA) kit (Cayman Chemical, Ann Arbor, United States), as previously described.<sup>16</sup> The levels below the detection limit (5 pg/ml) were arbitrarily assumed to be half of this value.

**Other biomarkers** SACE, S-Ca<sup>2+</sup>, and U-Ca<sup>2+</sup> were measured by colorimetry, and CRP by turbidimetric method. The laboratory specific normal limits were: 8–52 IU/l for SACE, 0–5 mg/l for CRP, 2.20–2.65 mmol/l for S-Ca<sup>2+</sup>, and <6.2 (women) or <7.5 (men) mmol/24 h for U-Ca<sup>2+</sup>.

**Lung high-resolution computed tomography** Lung high-resolution computed tomography (HRCT) was performed and the results were used for semiquantitative evaluation of parenchymal lesions (parenchymal score) and all intrathoracic lesions (total score – parenchymal lesions, hilar enlargement, and pleural lesions), according to Drent et al.<sup>22</sup>

**Statistical analysis** Quantitative data were presented as means with standard deviations. Comparisons of parameters between groups were performed with the use of  $\chi^2$  test for categorical data and nonparametric tests of significance for inter-

val data: the Mann-Whitney *U* test for comparison of distributions in 2 independent groups and Kruskal-Wallis in the case of more than 2 groups. The Spearman test was used for the calculation of correlations. Statistical significance was considered as  $P \leq 0.05$ . Calculations were performed using the Statistica 9.1 software.

**RESULTS** In patients with positive scintigraphy results, the indices calculated for regions of increased radiotracer uptake were between 1.5 and 3.0, with mean  $2.11 \pm 0.44$  (95% confidence interval, 1.91–2.30).

**TABLE 1** shows demographical, clinical, and radiological data of patients with negative and positive scintigraphy results. **TABLE 2** shows the results of lung function and laboratory tests. **FIGURE 1** shows positive uptake in the region of hilar lymph nodes. A detailed statistical analysis of HRCT pattern in relation to the results of scintigraphy was postponed due to the low number of patients with positive uptake in lung parenchyma (4 patients). The qualitative analysis of individual SPECT/CT scans justifies the conclusion that increased uptake is consistent with HRCT changes most typical for active parenchymal sarcoid lesions, such as diffuse micronodular (**FIGURE 2AB**) and consolidated infiltrates (**FIGURE 2CD**).<sup>22,23</sup> We were also able to show intensive parenchymal radiotracer uptake in a patient with destructive, emphysematous stage IV sarcoidosis (**FIGURE 2EF**), and no uptake in a patient chronically treated due to parenchymal infiltrations (not shown).

The groups were not different in terms of the lung function tests results; however, the trend was found towards higher radiotracer uptake in patients with bronchial obstruction ( $\text{FEV}_1/\text{FVC} < 0.7$ ). One patient with scintigraphic grade 0 and 6 patients with grade 1 had bronchial obstruction.

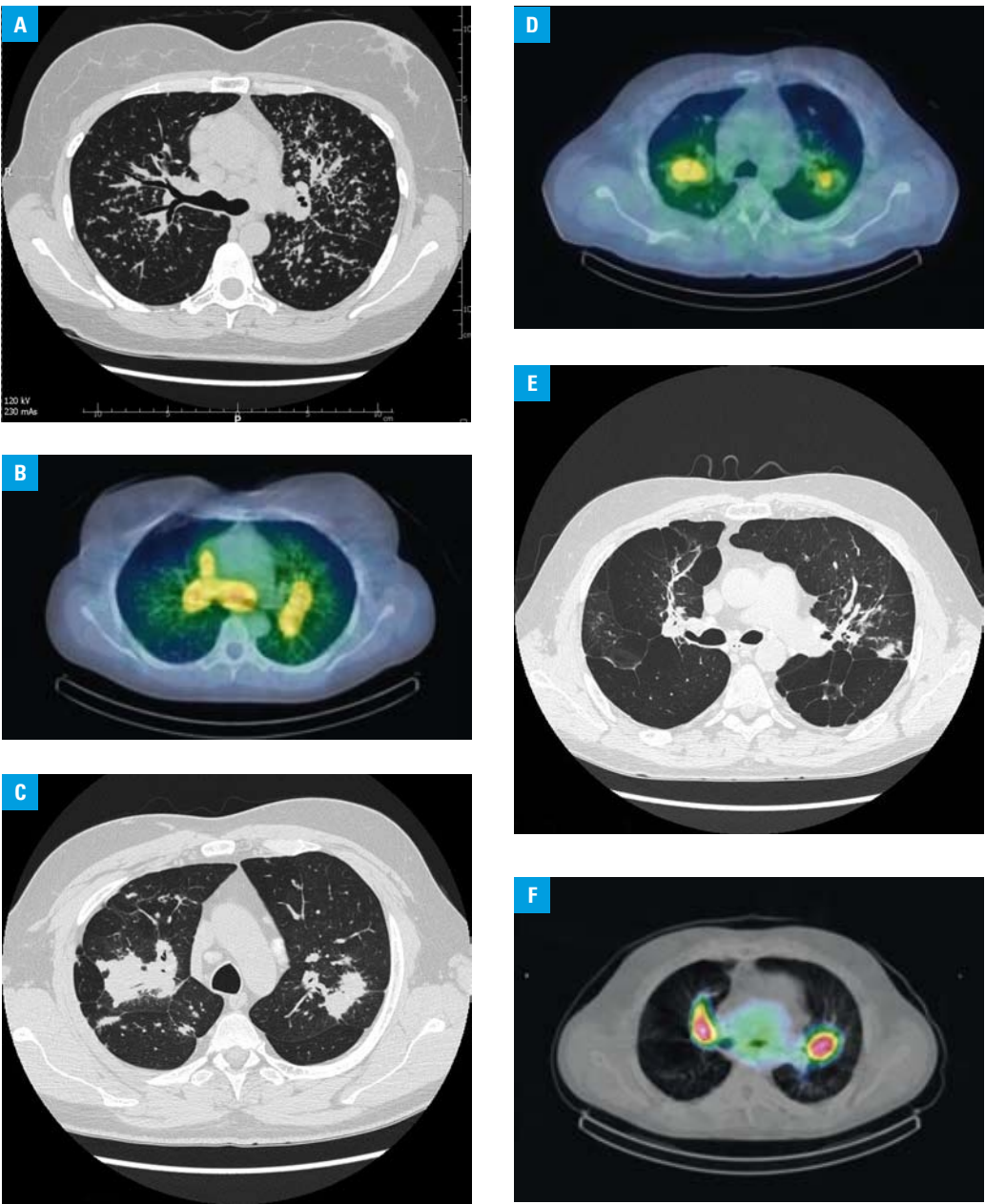
**TABLE 2** Lung function and laboratory parameters in the subgroups with grade 0 (negative radiotracer uptake) and 1 (positive radiotracer uptake)

Parameter	Grade 0 mean ± SD	Grade 1 mean ± SD	<i>P</i>
FVC, % pred.	101.3 ± 16.8	99.3 ± 15.3	0.86
FEV <sub>1</sub> , % pred.	92.8 ± 15.9	88.7 ± 18.8	0.51
FEV <sub>1</sub> /FVC, %	0.78 ± 0.12	0.74 ± 0.11	0.19
DLCOc, % pred.	91.7 ± 18.2	87.9 ± 12.9	0.82
SACE, IU/l	45.8 ± 17.8	65.5 ± 39.4	0.14
serum Ca <sup>2+</sup> , mmol/l	2.46 ± 0.08	2.47 ± 0.08	0.98
24-h urine Ca <sup>2+</sup> , mmol	7.66 ± 4.74	5.36 ± 2.48	0.16
CRP, mg/l	4.8 ± 7.7	12.3 ± 26.3	0.10
BALF lymphocytes, %	20.0 ± 15.0	30.0 ± 20.2	0.25
EBC 8-IP, pg/ml	5.4 ± 3.5	19.1 ± 19.8	0.023

Abbreviations: BALF – bronchoalveolar lavage fluid, CRP – C-reactive protein, DLCOc – diffusion capacity for carbon monoxide, corrected for hemoglobin, EBC 8-IP – exhaled breath condensate 8-isoprostane, FEV<sub>1</sub> – forced expiratory volume in 1 second, FVC – forced vital capacity, SACE – serum angiotensin-converting enzyme, others – see

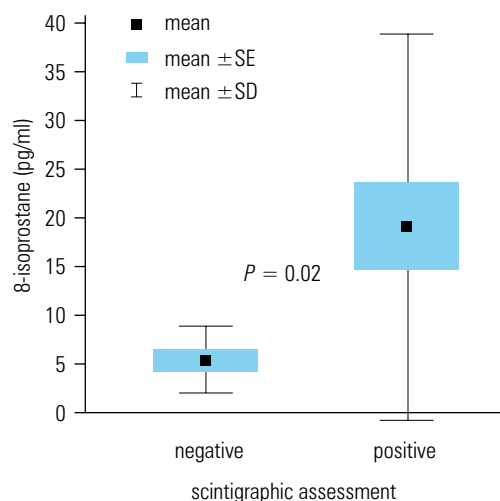
TABLE 1

**FIGURE 2** **A** Lung high-resolution computed tomography (HRCT) – multiple bilateral micronodular shadows and thickened peri-bronchial area typical for sarcoidosis **B** SPECT/CT (the same patient) – increased uptake of the tracer in hilar lymph nodes and surrounding lung parenchyma **C** Lung HRCT – bilateral massive consolidations with multiple satellite nodules – “galaxy lung” **D** SPECT/CT (the same patient) – increased uptake of the radiotracer in the involved area **E** A rare form of emphysematous changes with linear and consolidated infiltrations, suggestive of fibrosis in a patient suffering from chronic sarcoidosis **F** SPECT/CT (the same patient) – intensive radiotracer uptake in the region of consolidations



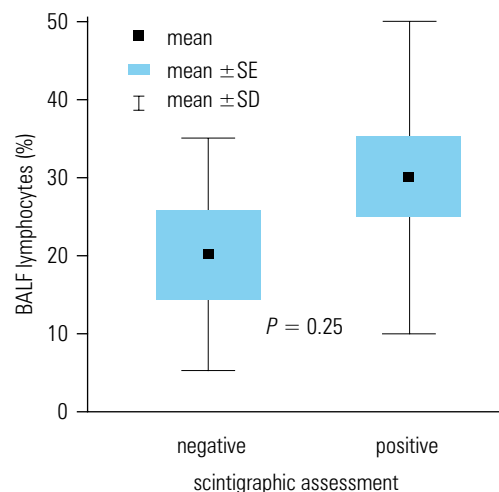
**FIGURE 1** Planar head and thorax somatostatin receptor scintigraphy; increased uptake of the tracer in the region of lung hili – stage I sarcoidosis





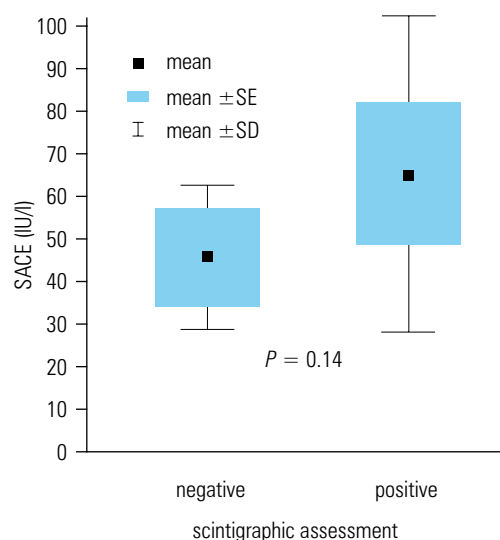
**FIGURE 3** Levels of 8-isoprostane in exhaled breath condensate in patients with negative and positive radiotracer uptake

Abbreviations: SD – standard deviation, SE – standard error



**FIGURE 5** Bronchoalveolar lavage fluid (BALF) lymphocytes in patients with negative and positive radiotracer uptake (nonsignificant)

Abbreviations: see TABLE 1 and FIGURE 3



**FIGURE 4** Serum angiotensin-converting enzyme (SACE) in patients with negative and positive radiotracer uptake (nonsignificant)

Abbreviations: see TABLE 1 and FIGURE 3

EBC 8-IP levels were significantly higher in patients with positive scintigraphy results than in patients with negative results ( $19.1 \pm 19.8$  vs.  $5.4 \pm 3.5$  pg/ml,  $P = 0.02$ , FIGURE 3). In none of the patients with negative scintigraphy results, the 8-IP was above 20 pg/ml, whereas such high 8-IP levels were detected in 5 of 18 patients with positive scintigraphy results and available EBC 8-IP data ( $P = 0.015$  by the  $\chi^2$  test comparing distribution of the results below 5 and above 20 pg/ml).

SACE levels were not significantly different between the groups (FIGURE 4):  $65.5 \pm 39.4$  vs.  $45.8 \pm 17.8$  IU/l for controls. In 2 patients with negative scintigraphy results, the SACE level was above the upper limit of normal (ULN). In 10 of 20 patients with positive radiotracer uptake, the SACE levels were below the ULN ( $P = 0.08$  by the  $\chi^2$  test).

S-Ca<sup>2+</sup> levels were within the normal limits in all patients. The results of U-Ca<sup>2+</sup> were not significantly different between the groups.

BAL was performed in 23 patients. The percentage of BALF lymphocytes was not significantly different between the groups ( $30.0 \pm 20.2$  vs.  $20.0 \pm 15.0$  for controls, FIGURE 5). In 3 of 16 patients with positive radiotracer uptake, BALF lymphocytes were less than 12%. In 1 of 7 patients with negative and 7 of 16 patients with positive scintigraphy results, BALF lymphocytes exceeded 25% of the cells ( $P = 0.12$  by the  $\chi^2$  test).

CRP levels were not different between the groups, and were above the ULN in 3 of 12 patients with scintigraphic grade 0 and in 8 of 18 subjects with grade 1 ( $P = 0.23$  by the  $\chi^2$  test).

We did not observe any effect of treatment on the above results.

In the group with positive radiotracer uptake, a statistically significant positive correlation was observed between the uptake ratio and SACE (FIGURE 6). Other correlations are presented in TABLE 3. Sensitivity, specificity, positive and negative predictive values for SACE, CRP, BALF lymphocytes, and EBC 8-IP are presented in TABLE 4.

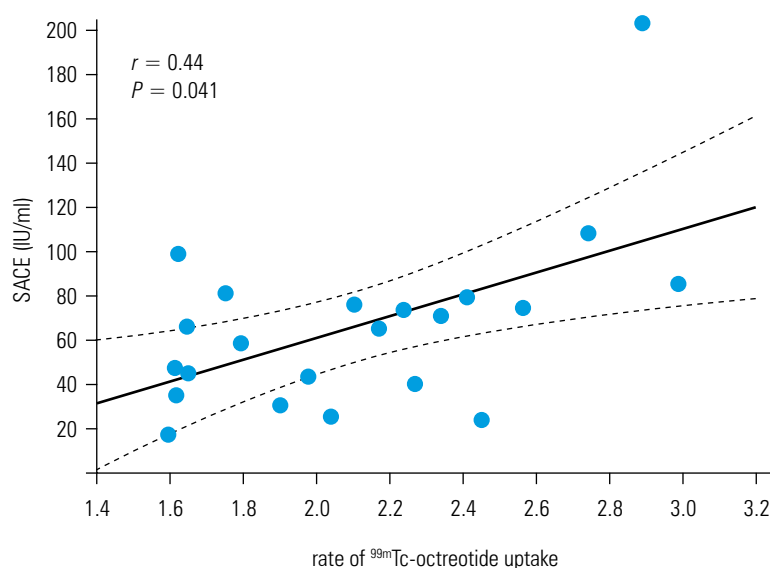
**DISCUSSION** For the purpose of this study, we used <sup>99m</sup>Tc-HYNIC-TOC scintigraphy as a reference method to evaluate the clinical usefulness of traditional markers, such as SACE, S-Ca<sup>2+</sup> levels, 24-hour U-Ca<sup>2+</sup> loss, CRP, and the percentage of lymphocytes in BALF, as well as of a novel marker of lipid peroxidation – 8-IP in EBC.

The only significant difference between scintigraphic negative vs. positive results was found in the level of EBC 8-IP. Unfortunately, this marker is not specific for sarcoidosis. For instance, it may be linked to intravascular oxidative stress and inflammation, processes leading to atherosclerosis and acute coronary events.<sup>24</sup> Earlier reports have already discredited 8-IP as a reliable

**TABLE 3** Correlations between the rate of  $^{99m}\text{Tc}$ -HYNIC-TOC uptake vs. laboratory and lung function parameters in the group of patients with positive scintigraphy

	n	r	P
SACE, IU/l	20	0.44	0.04
serum $\text{Ca}^{2+}$ , mmol/l	20	0.22	0.32
24-h urine $\text{Ca}^{2+}$ , mmol	18	0.04	0.86
CRP, mg/l	18	0.17	0.49
FVC, % pred.	20	0.01	0.96
FEV <sub>1</sub> , % pred.	20	-0.03	0.89
FEV <sub>1</sub> /FVC, %	20	-0.04	0.85
DLCOc, % pred.	15	-0.30	0.24
BAL lymphocytes, %	16	0.18	0.52
EBC 8-IP, pg/ml	18	-0.18	0.44

Abbreviations: see TABLES 1 and 2



**FIGURE 6** Serum angiotensin converting enzyme vs rate of radiotracer uptake in the group of patients with positive scintigraphy ( $r = 0.44$ ;  $P = 0.041$ )

marker of sarcoidosis activity, as it was shown to be low in a high proportion of patients with clinically active disease.<sup>17</sup> In this study, only when very high value (20 pg/ml) was taken as a cut-off point, the specificity and positive predictive value reached 100%, but it resulted in unacceptably low sensitivity and negative predictive value. In contrast to its low value as an activity marker, EBC 8-IP was shown to be elevated in patients with more advanced disease and low levels were shown to predict early remission.<sup>16,17</sup> These observations may illustrate the role of lipid peroxidation in chronic and progressive sarcoidosis. But still the practical meaning of high EBC 8-IP in sarcoidosis remains unclear.

SACE levels were not statistically different between the groups; however, a trend was observed towards higher levels in the group with positive radiotracer uptake. Moreover, we found the positive correlation between the radiotracer uptake and SACE levels. Kwekkeboom et al.,<sup>25</sup> who applied SR scintigraphy with the use of octreotide

found significant difference in SACE levels between patients with positive and negative radiotracer uptake. Our results confirmed the relatively low percentage of elevated SACE levels in active sarcoidosis, and are consistent with the results of other authors.<sup>6-8</sup> In addition, SACE was elevated in a proportion of patients with negative scintigraphy results, suggesting that elevated levels may persist in some patients with disease in remission. The level of SACE may be determined genetically, which may further complicate the interpretation of the results.<sup>26</sup> The increase of the percentage of lymphocytes in BALF, although not specific for sarcoidosis, was observed to be relatively sensitive for predicting disease activity in the previous studies.<sup>10</sup> Our results indicate that the increased percentage of BALF lymphocytes does not always discriminate active from inactive disease. Although the tendency was noticed towards higher percentage in patients with positive scintigraphy results, the statistical significance was not reached. Highly increased percentage of lymphocytes (>25%) was found in 1 patient with negative scintigraphy results. The persistence of lymphocytic alveolitis in clinically and radiologically inactive disease has been reported previously.<sup>12</sup> Intensive alveolitis was found only in 7 of 16 patients (44%), but lymphocyte percentage below 12% was found only in 3 of 16 patients (18%) with positive radiotracer uptake. BALF lymphocytes at the cut-off point of 12% showed the highest specificity, sensitivity, and positive and negative predictive value of all biomarkers examined in our study.

CRP is elevated in a large proportion of patients with sarcoidosis; however, due to lack of specificity its clinical value is limited. As reported by other investigators, it is usually elevated in patients with acute sarcoidosis, but frequently low in patients with chronic albeit active disease.<sup>29</sup> Moreover, markers of calcium metabolism have been shown to be useless in the evaluation of sarcoidosis activity.

These discrepancies between activity markers and scintigraphy results may also be related to mere scintigraphy. Low resolution may result in overlooking small extrapulmonary foci or tiny and diffuse lung parenchymal infiltrates. Due to physiologic uptake in several organs (i.e., liver, thyroid glands, urinary bladder), the detection of several extrapulmonary locations by this method is unfeasible. Finally, given low specificity, the detection signal may come from other inflammatory sites or cancer. Other methods, like positron emission tomography (PET) with the use of  $^{18}\text{F}$ -fluorodeoxyglucose, due to much higher sensitivity and improved resolution, may be more helpful in the evaluation of sarcoidosis.<sup>28</sup> New tracers, for instance L-3-[ $^{18}\text{F}$ ]-fluoro- $\alpha$ -methyltyrosine, are under evaluation, with the hope to improve differentiation between neoplastic and inflammatory lesions.<sup>29</sup> The role of PET in the clinical diagnosis and monitoring of sarcoidosis has increased in recent years, showing

**TABLE 4** Sensitivity, specificity, positive predictive value, and negative predictive value for serum angiotensin-converting enzyme (above the upper normal limit), C-reactive protein (above the upper normal limit), bronchoalveolar lavage fluid lymphocytes (>12%) and exhaled breath condensate 8-isoprostane (>20 pg/ml) as indicators of active sarcoidosis estimated on the basis of somatostatin scintigraphy results

	Sensitivity	Specificity	PPV	NPV
SACE, IU/l	50.0	81.8	83.3	47.4
CRP, mg/l	44.4	75.0	66.7	47.4
BALF lymphocytes, %	81.3	75.0	92.9	66.7
EBC 8-IP, pg/ml	27.8	100	100	45.8

Abbreviations: NPV – negative predictive value, PPV – positive predictive value, others – see TABLE 2

the practical need for implementation of imaging techniques in the evaluation of sarcoidosis. Unfortunately, in many countries indications to PET are limited almost exclusively to oncology, which results from high costs and low availability.

Finally, we managed to illustrate some important potential applications of somatostatin scintigraphy. Firstly, we showed the intensive uptake in lung parenchyma of a patient, who was diagnosed with stage IV sarcoidosis and who was primarily disqualified from the treatment (FIGURE 1EF). In consequence, treatment was restarted and partial resolution of parenchymal infiltrations was achieved. Secondly, prompted by scintigraphy results, we were able to stop the long-term treatment with oral steroids in a patient with extensive lung parenchymal infiltrations, which were negative on scintigraphy. On the basis of these 2 cases, we concluded that SR scintigraphy may be a valuable tool in discriminating inactive fibrotic/destructive changes from active inflammation. However, an independent study on the relationship between HRCT patterns and SR scintigraphy results, which would include a preselected population of patients with sarcoid parenchymal disease, should be performed in order to better define the potential usefulness of SR scintigraphy in the evaluation of parenchymal lesion activity. Szlubowski et al.<sup>30</sup> observed higher levels of tumor growth factor  $\beta$ , an important mediator of lung fibrosis, in the BALF of patients with diffuse parenchymal lung disease in the areas with high intensity of abnormalities assessed by HRCT. The above study shows the usefulness of HRCT scoring systems in the evaluation of the activity of lung parenchymal changes.

In summary, our results show that a single reliable test for estimation of activity in sarcoidosis does not exist. The diagnosis and estimation of activity should be based on a more complex evaluation, which should include clinical, radiological, and laboratory data. SR scintigraphy may be a valuable component of this complex evaluation, on condition that all its limitations are considered. The value of EBC 8-IP as an activity marker is low. However, the increased levels of this marker in selected patients with active sarcoidosis should be further studied in relation to the role of lipid peroxidation in the pathogenesis of chronic and progressive sarcoidosis.

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# Scyntygrafia receptorów somatostatynowych w sarkoidozie – związek z wybranymi markerami klinicznymi i laboratoryjnymi

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## SŁOWA KLUCZOWE

biomarkery,  
kondensat powietrza  
wydechowego,  
sarkoidoza,  
scyntygrafia  
receptorów  
somatostatynowych,  
8-isoprostan

## STRESZCZENIE

**WPROWADZENIE** Ocena aktywności procesu zapalnego w przebiegu sarkoidozy może stwarzać problemy w codziennej pracy klinicznej. Istnieje wiele biochemicznych markerów używanych w diagnostyce i monitorowaniu sarkoidozy. Scyntygrafia receptorów somatostatynowych z użyciem <sup>99m</sup>Tc-Tektrotydu może być stosowana do oceny aktywności procesu zapalnego.

**CELE** Celem pracy było ustalenie przydatności tradycyjnych biomarkerów (konwertazy angiotensyny w surowicy [serum angiotensin-converting enzyme – SACE], białka C-reaktywnego, markerów metabolizmu wapniowego, odsetka limfocytów w popłuczynach oskrzelowo-pęcherzykowych [bronchoalveolar lavage fluid – BALF]), a także nowego biomarkera, 8-isoprostanu (8-IP), w kondensacie powietrza wydechowego (exhaled breath condensate – EBC) w ocenie aktywności sarkoidozy, w odniesieniu do wychwyty radiofarmaceutyku w badaniu scyntygraficznym z użyciem analogu somatostatyny.

**PACJENCI I METODY** Badanie objęło 32 chorych na sarkoidozę. Badanie scyntygraficzne wykonano z użyciem analogu somatostatyny – <sup>99m</sup>Tc-HYNIC-TOC; rejestrowano obrazy w płaszczyźnie czołowej i połączone – SPECT/CT. Grupę badaną podzielono na podgrupy z dodatnim wychwytem znacznika (n = 20) i bez wychwyty (n = 12). Stężenia 8-IP w EBC mierzono za pomocą testu immunoenzymatycznego.

**WYNIKI** U chorych z dodatnim wychwytem znacznika stwierdzono znamienne wyższe stężenia 8-IP w EBC niż u chorych bez wychwyty (19,1 ± 19,8 vs 5,4 ± 3,5 pg/ml, p = 0,02). Stężenie SACE i odsetek limfocytów w BALF były również niezamiennie większe. W grupie chorych z dodatnimi wynikami scyntygrafii stwierdzono dodatnią korelację pomiędzy stopniem wychwyty znacznika a stężeniem SACE (r = 0,44, p = 0,041).

**WNIOSKI** Wyniki wskazują na małą wartość badanych markerów biochemicznych w ocenie aktywności choroby. Scyntygrafia receptorów somatostatynowych może mieć praktyczne zastosowanie w monitorowaniu sarkoidozy.

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