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^{18}F-FDG PET as a predictor of pulmonary function in sarcoidosis

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Abstract. *Purpose:* Fluor-18 fluorodeoxyglucose (^{18}F-FDG) PET is able to demonstrate sarcoidosis activity. Ongoing pulmonary sarcoidosis activity can be reflected by a decline in pulmonary function tests (PFT). To assess whether diffuse metabolic activity of the lung parenchyma imaged by ^{18}F-FDG PET predicts future pulmonary deterioration, ^{18}F-FDG PET was compared with PFT. *Methods:* In this retrospective cohort study, 43 newly diagnosed, sarcoidosis patients were analyzed. Based on ^{18}F-FDG PET, patients were diagnosed with diffuse parenchymal disease activity, without or with immunosuppressive treatment, started after ^{18}F-FDG PET was performed. As a control, sarcoidosis patients with mediastinal/hilar disease activity but without metabolic activity in the lung parenchyma were analyzed, all without treatment. Vital capacity (VC), forced expiratory volume (FEV_1) and diffusion capacity of the lung for carbon monoxide (DLCO) were analyzed per group at baseline, i.e. at the time ^{18}F-FDG PET was performed, and after one year follow-up. *Results:* At follow-up, a significant decrease in DLCO was found in untreated patients with diffuse parenchymal activity. No change in VC or FEV_1 could be observed. Treated patients with parenchymal activity showed a significant increase in VC, FEV_1 and DLCO, while patients without parenchymal activity did not show any change in PFT. *Conclusions:* In sarcoidosis, diffuse parenchymal disease imaged by ^{18}F-FDG PET, predicts a future deterioration of DLCO when untreated. Treatment however, improves VC, FEV_1 and DLCO significantly suggesting that ^{18}F-FDG PET represents the pulmonary improvement that can be achieved. The absence of metabolic activity in the lung parenchyma justifies a wait-and-see policy. *(Sarcoidosis Vasc Diffuse Lung Dis 2011; 28: 123-129)*

Key words: sarcoidosis, ^{18}F-FDG PET, pulmonary function tests

Introduction

The lung is the most frequently affected organ in sarcoidosis (1, 2). The characteristic non caseating epitheloid cell granuloma can be found in intra thoracic lymph nodes as well as the lung parenchyma. Thoracic involvement of sarcoidosis is reflected by conventional chest radiography and can be classified into five stages. Stage 0 is defined as normal, stage I disease as bihilar lymphadenopathy, stage II as bihilar lymphadenopathy combined with parenchymal involvement, stage III as exclusive parenchymal involvement and stage IV as fibrosis (3). Each radiological stage correlates with a certain spontaneous remission rate of sarcoidosis. The higher the stage, the lower the spontaneous recovery rate (4).

Pulmonary function tests (PFT) may be abnormal in sarcoidosis, particularly the diffusion capacity

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of the lung for carbon monoxide (5). Remarkably, PFT does not correlate with the radiographic abnormalities. Abnormal PFT can be found in patients without parenchymal involvement and vice versa (6). However, serial PFT is suggested to be used in monitoring disease progression (6). PFT reflects the actual involvement of pulmonary tissue. Therefore, the disease needs to progress first before it becomes evident. A tool, adequately assessing the actual presence of active pulmonary disease, might be desirable since active sarcoidosis may require therapeutic intervention.

Fluor-18 fluorodeoxyglucose (^{18}F-FDG) PET is an in vivo imaging technique and has proven to be useful in depicting sarcoidosis activity (7-9). However, ^{18}F-FDG PET with regard to clinical outcome has not been evaluated yet. This study was performed to evaluate the significance of parenchymal activity with regard to future pulmonary function.

Methods

Patients

In this retrospective cohort study, 49 consecutive patients with newly diagnosed and histologically proven sarcoidosis were evaluated. The patients were seen at the department of pulmonology of the St. Antonius Hospital between January 2004 and December 2009. The diagnosis of sarcoidosis was based on clinical findings, supported by histological evidence and after the exclusion of other known causes of granulomatosis in accordance with the consensus statement on sarcoidosis of the ATS/ERS/WASOG (1).

Patients underwent PFT and ^{18}F-FDG PET as part of their routine analysis, and none of them used immunosuppressive treatment. Patients were grouped based on the results of ^{18}F-FDG PET with regard to lung parenchymal activity. Group A consisted of patients with diffusely increased metabolic activity in the lung parenchyma without the use of corticosteroids or immunosuppressive drugs during follow-up. Patients in group B showed diffuse parenchymal activity and received corticosteroids or immunosuppressive drugs after ^{18}F-FDG PET was performed. The pulmonologist decided whether treatment was indicated, based on a combination of symptoms, clinical findings, PFT, serological markers and ^{18}F-FDG PET.

Group C was the control group, consisting of patients with increased metabolic activity in the mediastinum and hila but without activity in the lung parenchyma. These patients did not receive treatment during follow-up. Chest radiographic stage according to Scadding was evaluated (3). This study was approved by the local medical ethical committee.

Serum markers

ACE and sIL-2R were analyzed and compared between the groups. ACE level was considered positive or negative in accordance with genotype corrected reference values. A for genotype corrected ACE was calculated and expressed as Z-score (10). Serum sIL-2R above 700 U/ml was considered increased.

Pulmonary Function Tests

VC, FEV_1 and DLCO were evaluated at baseline, i.e. at the time ^{18}F-FDG PET was performed, and after one year follow-up. For follow-up, a time interval of 10-14 months was allowed. In patients requiring prednisone or immunosuppressive drugs before follow-up was completed, PFT performed at that time was used as follow-up.

Absolute change in percentage of predicted VC, FEV_1 and DLCO was calculated per group and corrected for the time of inclusion. Spirometry was performed in accordance with the guidelines provided by the ERS (11-13). DLCO was corrected for the hemoglobin concentration. VC, FEV_1 and DLCO were determined by using a MS-PFT analyzer unit (Jaeger, Würzburg, Germany).

^{18}F-FDG PET

The patient fasted for at least six hours and before the intravenous injection of ^{18}F-FDG, 5 milligram of diazepam was administered to reduce muscle activity and accumulation of ^{18}F-FDG in brown fat. In order to reduce radiation exposure and accelerate ^{18}F-FDG excretion by the kidneys, 20 milligrams of furosemide was injected intravenously. Subsequently, 295-400 MBq ^{18}F-FDG (Covidien, Petten, the Netherlands) was administered intravenously, depending on the patients' body weight. PET was performed using the Philips Allegro PET system with external Cesium-137 source for transmission scanning (Philips Medical Systems, Eindhoven, the Netherlands). Sixty minutes after administration of

^{18}F-FDG, transmission scan was started with a transmission time of 23 seconds per bed position. Emission scan was performed from the subinguinal region to the head with an acquisition time of three minutes per bed position. Reconstruction was performed in accordance with the 3D-RAMLA protocol applying 4 iterations with a 144 x 144 matrix (14).

Two experienced, independent nuclear medicine physicians interpreted ^{18}F-FDG PET. Diffusely affected lung parenchyma was present when at least two third of the lung parenchyma showed an increased metabolic activity. The degree of increased metabolic activity may vary but needed to be higher than the mediastinal background, i.e. the blood pool. Maximum Standardized Uptake Value (SUV_{max}) was calculated in the mediastinum/hilar region as well as in the lung parenchyma. Regions of interest (ROI) were drawn over the visually affected part of the organ to measure SUV_{max} by an automatic ROI drawing program provided by Hermes Diagnostics.

Statistical analysis

Continuous data were expressed as mean values ± SD or median (interquartile range) where appropriate. Categorical data were analyzed by chi-square and continuous data by ANOVA with a Tukey HSD post hoc test were appropriate. Changes in VC, FEV_1 and DLCO were normalized per time unit (months) and expressed as percentage predicted. The Kruskal-Wallis test was used to assess ACE values between the groups with an additional Mann-Whitney test. To assess the predictive value of the PET stage, SUV_{max}, ACE and sIL-2R, ANOVA with a LSD post hoc test was performed. The statistical evaluation was performed using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Patients

Of the 49 analyzed patients, 5 patients with exclusive mediastinal/hilar activity were lost to follow-up. Control PFT was performed in these patients but the time interval was less than 12 months. One patient with diffuse parenchymal activity on ^{18}F-FDG PET and prednison was excluded because of a severe pneumonia with prolonged pulmonary deterioration. Therefore, 43 patients were included in this analysis. Group A consisted of 11 patients and group B and C of 16 patients each. In Table 1, base-

Table 1. Patient characteristics at baseline

	Group A Parenchymal activity, untreated	Group B Parenchymal activity, treated	Group C No parenchymal activity
Number of patients	*n = 11*	*n = 16*	*n = 16*
Age	43.2 ± 9.5	40.8 ± 11.0	46.1 ± 11.6
Female sex (%)	5 (46%)	7 (44%)	4 (25%)
Chest radiography	2.1 ± 0.3	2.4 ± 0.8	1.5 ± 0.9
Stage 0	0	0	1
Stage I	0	1	9
Stage II/III	11	13	6
Stage IV	0	2	0
PFT			
VC	89.0 ± 17.9	80.4 ± 18.4	102.1 ± 12.0
FEV_1	86.9 ± 15.7	72.1 ± 21.5	94.0 ± 11.2
DLCO	80.7 ± 13.8	64.6 ± 9.5 *	87.0 ± 14.4
ACE Z-score	1.6 (0.8-3.0)	3.4 (2.4-9.6) †	1.1 (0.2-1.7)
sIL-2R	810 ± 278	1603 ± 893 †	1001 ± 657
SUV_{max} mediastinum/hila	5.7 ± 2.1	5.7 ± 2.8	10.2 ± 7.6
SUV_{max} lung parenchyma	6.9 ± 3.3	7.2 ± 3.2	1.2 ± 0.3

Data are presented as the mean ± SD or median (interquartile range). Pulmonary function tests (PFT) are presented as the percentage predicted. VC = vital capacity, FEV_1 = forced expiratory volume in 1 second, DLCO = diffusion capacity of the lung for carbon monoxide, ACE Z-score = angiotension converting enzyme corrected for genotype, sIL-2R = soluble interleukin-2 receptor.
Group A vs. B: * = $p < 0.01$ and † = $p < 0.05$

line characteristics of the 43 sarcoidosis patients are summarized. In all patients, histological confirmation of sarcoidosis was obtained within 2.7 weeks (range 0-11 weeks) of ^{18}F-FDG PET. In group A, 4 patients required immunosuppressive drugs before the follow-up of 12 months was completed. In the control group, no immunosuppressive drugs were started.

According to the chest radiographic stages, there was one patient with stage 0 disease. In 10 patients, sarcoidosis was limited to hilar lymph nodes (stage I) and 30 patients did have parenchymal abnormalities (stage II/III). Two patients had signs of fibrosis (stage IV). All patients in group A and B showed a radiographic stage of ≥ 2, except one. Consequently, 6 patients in group C showed a radiographic stage of ≥ 2. The radiographic stages per group are demonstrated in Table 1.

Overall, ACE was increased in 23 patients (54%) and sIL-2R was increased in 27 patients (63%). In group A, both ACE and sIL-2R were increased in 5 patients (45%). In group B, ACE and sIL-2R was increased in 14 patients (88%) and 13 patients (81%), respectively. In group C, increased ACE was present in 4 patients (25%) and increased sIL-2R in 9 (56%) patients. ACE and sIL-2R differed between the groups ($p < 0.001$ and $p < 0.05$, respectively) with a significant difference for both parameters between group A and B (both $p < 0.05$).

Patients in group B received therapy, based on progressive (pulmonary) symptoms combined with severe impaired baseline PFT in 10 patients. Extra pulmonary disease requiring therapy was present in three patients and hypercalcaemia in one. One patient demonstrated severe endobronchial involvement. Chest radiography revealed signs of fibrosis in two patients. In these patients, therapy was started because of the symptoms combined with increased serum markers.

^{18}F-FDG PET

Group A consisted of 11 patients. In 8 patients (73%), extra pulmonary lesions were found. SUV_{max} was 5.7 (± 2.1) in the mediastinum/hilar region and 6.9 (± 3.3) in the lung parenchyma. Group B consisted of 16 patients. Extra pulmonary lesions were found in 15 patients (94%). The difference in extra pulmonary findings between group A and B was not significant ($p = 0.13$). SUV_{max} was 5.7 (± 2.8) in the

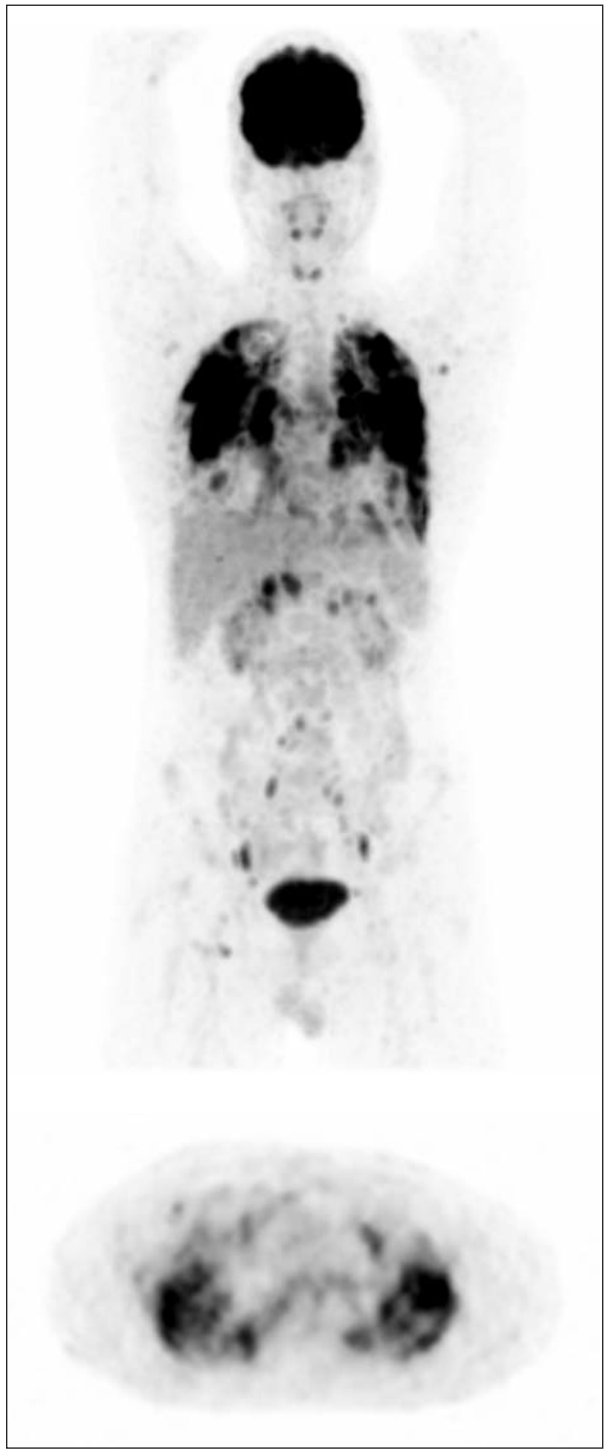

Fig. 1. ^{18}F-FDG PET demonstrating diffuse metabolic activity in the lung parenchyma. Furthermore, increased activity is seen in lymph nodes in the hila, mediastinum and extra pulmonary regions. Eight months after ^{18}F-FDG PET was performed, VC, FEV_1 and DLCO showed a decrease of 10%, 8% and 15%, respectively.

mediastinum/hilar region and 7.2 (± 3.2) in the lung parenchyma. Group C consisted of 16 patients and extra pulmonary lesions were found in 8 (50%). SUV_{max} was 10.2 (± 7.6) in the mediastinum/hilar region and 1.2 (± 0.3) in the lung parenchyma.

SUV_{max} in the lung parenchyma differed between the groups ($p < 0.01$), but not between group A and B ($p = 0.87$). No differences were found in SUV_{max} of the mediastinum/hila between the groups ($p = 0.14$). In Figure 1, ^{18}F-FDG PET of a patient in group A is shown.

Pulmonary function tests

Baseline PFT was performed within 2 weeks of ^{18}F-FDG PET (range -10 weeks-5 weeks).The median time interval between follow-up PFT and ^{18}F-FDG PET was 11.7 months (range 7-14 months).

At baseline, there was a difference in VC, FEV_1 and DLCO between the groups ($p < 0.01$ for all). Group A and B did not differ significantly in VC and FEV_1, but they differed in DLCO ($p < 0.01$).

PFT results at baseline and follow-up are presented in Table 2. In untreated patients with parenchymal activity (group A), no change in VC or FEV_1 was found after one year, but there was a significant decrease in DLCO of 7.8% (± 7.1%). Prednisone was started in 4 patients before follow-up was completed (range 7-11 months). Three patients showed non-significant decreasing PFT, progressive dyspnoea, worsening chest radiography and increasing serological markers. One patient had stable PFT and no pulmonary symptoms. Because of progressive arthralgia and worsening chest radiography, prednisone was started.

In group B, all patients were treated after ^{18}F-FDG PET was performed. One patient received methotrexate given the presence of severe osteoporosis. All other patients received prednisone. In these patients, improvement of VC, FEV_1 and DLCO was seen after one year. The increase in VC was 11.6% (± 11.2%), in FEV_1 9.4% (± 10.0%) and in DLCO 8.7% (± 8.0%). The improvement was significant for all lung functional parameters ($p < 0.01$).

In patients without parenchymal activity (group C), no changes in PFT could be found.

Corrected for the time of inclusion, PFT of all groups was compared. Box-and-whisker diagrams of the change in VC, FEV_1 and DLCO per time unit are shown in Figure 2.

Comparing group A and C, there was a significant decrease in DLCO in patients with diffuse parenchymal activity ($p < 0.01$), but no change in VC or FEV_1 could be observed.

Patients in group B showed a significant increase of VC, FEV_1 and DLCO compared to group C.

Baseline ACE, sIL-2R, the presence of parenchymal activity by PET and SUV_{max} in the lung parenchyma and mediastinum/hila were assessed with regard to their predictive value in lung functional outcome. The PET pattern showed to be a predictive factor for the change in VC and DLCO ($p < 0.05$ and $p < 0.01$, respectively). ACE predicted the change in DLCO ($p < 0.05$).

Discussion

In the current study, intra-thoracic metabolic activity imaged by ^{18}F-FDG PET was correlated with PFT in newly diagnosed, pulmonary sarcoidosis patients. The presence of diffusely increased metabolic activity in the lung parenchyma correlated with a future decrease in DLCO when untreated. Such a correlation could not be found for VC or FEV_1. Patients with diffuse active disease in the lung

Table 2. PFT at baseline and one year follow-up in patients with and without metabolic activity in the lung parenchyma based on ^{18}F-FDG PET

	VC baseline	VC follow-up	*p*	FEV_1 baseline	FEV_1 follow-up	*p*	DLCO baseline	DLCO follow-up	*p*
Parenchymal activity, untreated	89% (± 18)	88% (± 20)	ns	87% (± 16)	87% (± 20)	ns	81% (± 14)	73% (± 13)	< 0.05
Parenchymal activity, treated	80% (± 18)	92% (± 12)	< 0.01	72% (± 22)	82% (± 19)	< 0.01	65% (± 9)	72% (± 11)	< 0.01
No parenchymal activity	102% (± 12)	102% (± 11)	ns	94% (± 11)	94% (± 10)	ns	87% (± 14)	89% (± 14)	ns

Data are presented as the mean ± SD. Pulmonary function tests are presented as the percentage predicted.
VC = vital capacity, FEV_1 = forced expiratory volume in 1 second, DLCO = diffusion capacity of the lung for carbon monoxide, ns = not significant

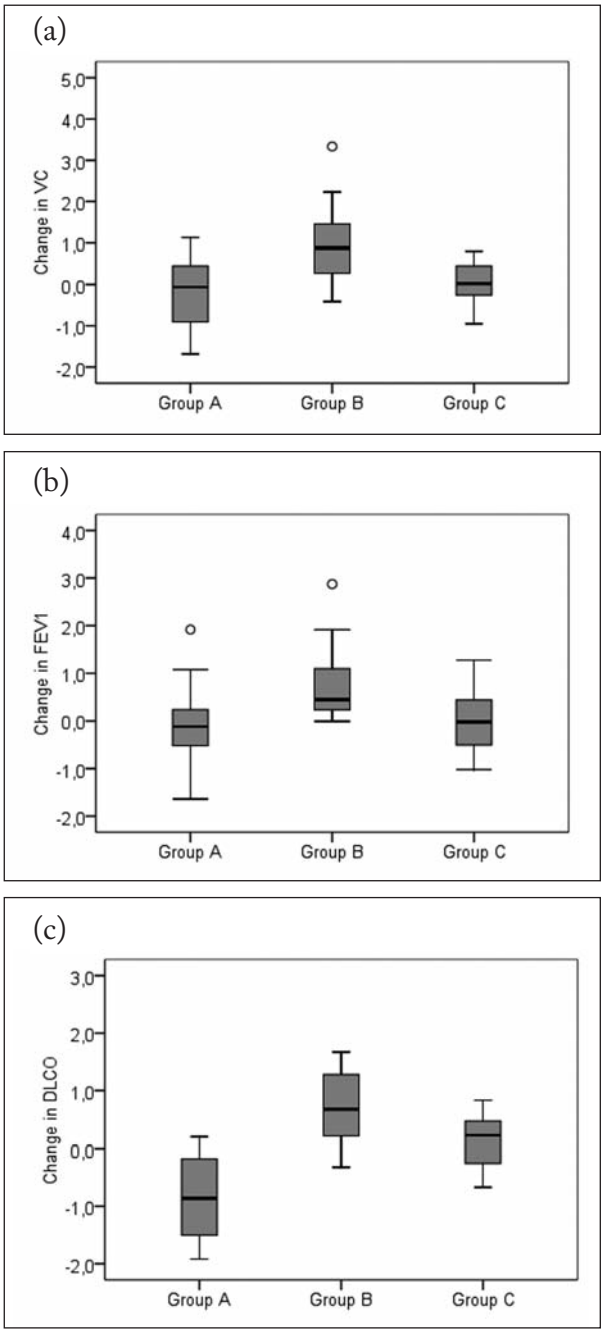

Fig. 2. Box and whisker diagram of the change in VC (a), FEV_1 (b) and DLCO (c), expressed as % predicted per month.
Group A = parenchymal activity untreated; Group B = parenchymal activity treated, Group C = no parenchymal activity

parenchyma receiving corticosteroids or immunosuppressive drugs showed a significant increase in VC, FEV_1 and DLCO. Furthermore, patients without increased metabolic activity in the lung parenchyma showed stable lung function tests during follow-up.

This is the first study, assessing the presence of ^{18}F-FDG activity in sarcoidosis patients with regard to clinical outcome. The current data support the hypothesis that increased metabolic activity in the lung parenchyma represents active disease since a decline in DLCO was observed. Intervention was required in 4 patients (36%) with diffuse parenchymal activity. Conversely, patients without metabolic activity in the lung parenchyma showed stable PFT after one year. A wait-and-see policy appears to be justified in the absence of parenchymal activity while a regular PFT during follow-up is required in patients with active parenchymal disease. In patients with pulmonary involvement receiving corticosteroids or other immunosuppressive drugs, a significant improvement of PFT was found. All patients exhibited ongoing inflammatory activity in the lung parenchyma as shown by ^{18}F-FDG PET, implying that metabolic active disease correlates with reversible abnormalities.

Serial PFT is advised to monitor disease progression since a decrease in PFT suggests pulmonary activity. However, the use of serial PFT might have limitations since a pulmonary decline only becomes evident when sarcoidosis has progressed and the patient has deteriorated. This clinical worsening may consist of disabling symptoms and impair the quality of life. Impaired quality of life frequently includes a reduced working capacity, all in a predominantly young population (15).

In our study, a selected patient population was observed. Patients with diffusely affected lung parenchyma were included. The inclusion criterion was restricted to this specific pulmonary pattern, since quantitative analysis of the affected lung parenchyma is not possible yet. When the extent of affected tissue could be quantified, the degree of metabolic activity can be taken into account. The currently available PET/CT systems might offer a solution for disease quantification. However, when quantification models become accessible, additional research is required to determine the significance of partly increased metabolic activity in the lung parenchyma.

There was a significant difference in DLCO, serum ACE and sIL-2R between group A and B at baseline. Increased ACE and sIL-2R, biomarkers for active sarcoidosis, combined with lower PFT might

explain the urge for treatment in group B. Based on [18]F-FDG PET, patients in group A and B demonstrated a similar pulmonary involvement. Apparently, [18]F-FDG PET is unable to distinguish patients with regard to baseline PFT. Disease duration might clarify these differences since patients delay can already have caused a decrease in PFT.

Serum ACE and sIL-2R was significantly higher in patients receiving treatment after [18]F-FDG PET. The amount of ACE and sIL-2R is suggested to be related with the total granuloma load and total T cell activity, respectively (16, 17). Indeed, besides pulmonary involvement, [18]F-FDG PET demonstrated active extra pulmonary lesions in 94% of the patients receiving treatment, while this was 73% in untreated patients. Although this might suggest that the total granuloma load is larger in the treated group, the difference in extra pulmonary findings was not significant. In addition, the extra pulmonary findings were not quantified.

A previous study has shown that normal ACE and sIL-2R does not rule out active disease (18). Indeed, the majority of untreated patients with diffuse parenchymal disease did not have increased serum levels while a significant decrease in DLCO after one year was found. Since diffuse lung parenchymal activity was demonstrated by [18]F-FDG PET, it appears that this nuclear imaging technique more adequately reflects the actual pulmonary parenchymal activity state of sarcoidosis than serum markers.

Based on [18]F-FDG PET patterns, patients were assigned to different groups. The control group consisted of patients with mediastinal and hilar lymph nodes without parenchymal activity, implying stage I disease on chest radiography. However, radiography revealed stage II or III disease in 6 patients (38%) while PFT did not change during follow-up. This finding is in line with previous studies describing that PFT is not related with pulmonary abnormalities on radiography (6), and might suggest that [18]F-FDG PET more adequately reflects the presence of clinical relevant active disease than chest radiography.

In conclusion, diffuse parenchymal activity in sarcoidosis patients, imaged by [18]F-FDG PET, predicts a future deterioration of DLCO when medical treatment is withheld. Treatment however, improves VC, FEV_1 and DLCO significantly. In sarcoidosis patients without metabolic activity in the lung parenchyma, a wait-and-see policy seems allowed even in patients with radiographic signs of parenchymal disease.

Reference

1. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999; 160 (2): 736-55.
2. Lynch JP, III, Ma YL, Koss MN, White ES. Pulmonary sarcoidosis. Semin Respir Crit Care Med 2007; 28 (1): 53-74.
3. Scadding JG. Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation. Br Med J 1961; 2 (5261): 1165-72.
4. Neville E, Walker AN, James DG. Prognostic factors predicting the outcome of sarcoidosis: an analysis of 818 patients. Q J Med 1983; 52 (208): 525-33.
5. Boros PW, Enright PL, Quanjer PH, Borsboom GJ, Wesolowski SP, Hyatt RE. Impaired lung compliance and DLCO but no restrictive ventilatory defect in sarcoidosis. Eur Respir J 2010.
6. Winterbauer RH, Hutchinson JF. Use of pulmonary function tests in the management of sarcoidosis. Chest 1980; 78 (4): 640-7.
7. Braun JJ, Kessler R, Constantinesco A, Imperiale A. (18)F-FDG PET/CT in sarcoidosis management: review and report of 20 cases. Eur J Nucl Med Mol Imaging 2008; 35 (8): 1537-43.
8. Teirstein AS, Machac J, Almeida O, Lu P, Padilla ML, Iannuzzi MC. Results of 188 whole-body fluorodeoxyglucose positron emission tomography scans in 137 patients with sarcoidosis. Chest 2007; 132 (6): 1949-53.
9. Yamada Y, Uchida Y, Tatsumi K et al. Fluorine-18-fluorodeoxyglucose and carbon-11-methionine evaluation of lymphadenopathy in sarcoidosis. J Nucl Med 1998; 39 (7): 1160-6.
10. Kruit A, Grutters JC, Gerritsen WB, et al. ACE I/D-corrected Z-scores to identify normal and elevated ACE activity in sarcoidosis. Respir Med 2007; 101 (3): 510-5.
11. MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005; 26 (4): 720-35.
12. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005; 26 (2): 319-38.
13. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J 2005; 26 (1): 153-61.
14. Boellaard R, Oyen WJ, Hoekstra CJ, et al. The Netherlands protocol for standardisation and quantification of FDG whole body PET studies in multi-centre trials. Eur J Nucl Med Mol Imaging 2008; 35 (12): 2320-33.
15. De Vries J, Drent M. Quality of life and health status in sarcoidosis: a review. Semin Respir Crit Care Med 2007; 28 (1): 121-7.
16. Ainslie GM, Benatar SR. Serum angiotensin converting enzyme in sarcoidosis: sensitivity and specificity in diagnosis: correlations with disease activity, duration, extra-thoracic involvement, radiographic type and therapy. Q J Med 1985; 55 (218): 253-70.
17. Keicho N, Kitamura K, Takaku F, Yotsumoto H. Serum concentration of soluble interleukin-2 receptor as a sensitive parameter of disease activity in sarcoidosis. Chest 1990; 98 (5): 1125-9.
18. Keijsers RG, Verzijlbergen FJ, Oyen WJ, et al. 18F-FDG PET, genotype-corrected ACE and sIL-2R in newly diagnosed sarcoidosis. Eur J Nucl Med Mol Imaging 2009; 36 (7): 1131-7.