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Pulmonary Function Tests and Carbon Monoxide Transfer Coefficient Assessment of Sarcoidosis Patients in Regard to Prognosis

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Abstract

The aim of our study was to determine the utility of the PFTs [Pulmonary Function Tests (PFTs)] and DLCO/VA [Diffusion Capacity/alveolar Volume (DLCO/VA)] in regard to the clinical prognosis of sarcoidosis patients. Another objective was to assess the prognostic significance of PFTs, DLCO/VA, extrapulmonary organ and endobronchial involvement when these features were evaluated in collaboration.

One hundred ninety four sarcoidosis patients underwent PFT, DLCO/VA, thorax CT and bronchoscopy. Extrapulmonary organ involvement was classified into two groups as limited if less than two and as extensive if three or more extrapulmonary organs were involved. Endobronchial disease was denoted as limited if one bronchial biopsy site was positive and as diffuse if more than two biopsy sites were positive histopathologically. Sarcoidosis activity was evaluated in regard to progressive stage, detoriation of pulmonary function tests, permanent decline of DLCO/VA values, and the presence of severe systemic symptoms, significant laboratory manifestations and extrapulmonary organ involvement. Low PFTs and DLCO/VA values were more frequent in patients with extensive organ and diffuse endobronchial involvement in chronic persistent disease.

We conclude that PFTs and DLCO/VA may be used as decisive clinical markers to predict the prognosis of sarcoidosis patients. PFTs and DLCO/VA alone do not reveal a statistically significant determination for evaluating the prognosis of sarcoidosis. If PFTs and DLCO/VA are utilized along with extrapulmonary organ and endobronchial involvement, considerably high levels of statistical significance for the assessment of prognostic outcome may be obtained. These tests prove to be a useful diagnostic utility with easy clinical applicability to appraise the prognostic outcome of sarcoidosis patients. PFTs and DLCO/VA reval note worthy conclusions for prognosis if they are assessed in collaboration with the disease extensity other than the trivial clinical manifestations.

Keywords: Sarcoidosis; Prognosis; Pulmonary function tests; Diffusion capacity

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Introduction

The extent, the severity of lung involvement and the prognostic assessment of sarcoidosis patients is a difficult task for the pulmonary clinician. (PFTs) [Pulmonary Function Tests (PFTs)] and DLCO/VA [Diffusion capacity/alveolar volume (DLCO/VA)] are done to evaluate the degree of respiratory impairment initially and to monitor the disease course with sequential measurements thereafter. PFTs may not be reliable for detecting parenchymal involvement in sarcoidosis nor they establish an accurate forecast for the extent of parenchymal disease [1,2]. PFTs typically reveal a restrictive pattern with a reduction in DLCO/VA in sarcoidosis. Approximately 20% of patients with stage I sarcoidosis have abnormal PFTs while they are abnormal in 40 to 70% of the patients with stage II to IV. Reduction of lung volumes, particularly the FVC [Forced Vital Capacity (FVC)] is notably common and reveals a marked reduction from stage I to stage IV with significant overlaps at the individual level [1-3]. Reduction of DLCO/VA is the most frequent respiratory functional impairment and the severity of detoriation correlates well with the fibrotic honeycomb parenchymal lesions identified by the computed tomography [4].

Although there are many previous studies relevant to PFTs and DLCO/VA evaluation in

sarcoidosis that establish the clinical utility of the pulmonary function tests [1-4], the clinicians do not have an accurate or adequate knowledge about the consistency and the predictive quality of these tests because their usefulness is still indistinct and deficient in regard to clinical manifestations, prognosis, extrapulmonary organ and endobronchial sarcoidosis involvement. The aim of our study is to define the clinical utility of PFTs and DLCO/VA when they are appraised along with the extrapulmonary organ and the endobronchial sarcoidosis involvement to determine their accuracy for prognosis more accurately in sarcoidosis patients other than the conventional means or the orthodox clinical manifestations.

Materials and Methods

This is a retrospective cohort study including 194 sarcoidosis patients who were evaluated between March 1984 and April 2019 at our center. The study has been approved by the IRB/Ethics Committee of Cerrahpasa Medical Faculty (02/03/2016-82580). All patients fulfilled the American Thoracic Society/European Respiratory Society criteria of sarcoidosis [5-7]. The patients underwent PFTs, DLCO/VA, chest X-ray, FOB [Fiber Optic Bronchoscopy (FOB)], and thorax CT [Computed Tomography (CT)]. Laboratory investigations included complete blood count, urine analysis, serum Ca, 24-h urinary Ca, erythrocyte sedimentation rate, C-reactive protein, serum ACE [Angiotensin-Converting Enzyme (ACE)] and liver and renal function tests. Abnormal liver or renal function tests, serum ACE, hypercalcemia and hypercalciuria were present if they were above the normal limit values. DeRemee criteria were as follows; stage 0: normal, stage 1: bilateral hilar lymphadenopathy, stage 2: bilateral hilar lymphadenopathy and parenchymal involvement, stage 3: parenchymal involvement only and stage 4: pulmonary fibrosis [8] was used for the radiologic stage evaluation of sarcoidosis. Patients with a smoking history and patients with a current or a previous lung disease were excluded from the study.

PFTs and DLCO/VA were carried out according to the ATS/ERS criteria. The PFTs were assessed according to the ATS guidelines [9]. Single-breath technique was utilized for DLCO/VA measurement that was adjusted for alveolar ventilation. PFTs and DLCO/VA were appraised as abnormal if they were off the 95% confidence interval of the predicted estimates. Restrictive lung disease was designated by a decreased TLC [Total Lung Capacity (TLC)] or FVC [Forced Vital Capacity (FVC)] with a normal or a high FEV1/FVC [Forced Expiratory Volume in one second to Forced Vital Capacity ratio (FEV1/FVC)]. PFTs and DLCO/VA were evaluated in regard to decreased percentage rates according to the predicted normal values. A FVC, a TLC or a DLCO/VA percentage value below 80% was determined as abnormal. For the evaluation of systemic sarcoidosis and extrapulmonary organ involvement all patients were screened by a dermatologist, neurologist and an ophthalmologist. The patients were also evaluated for the development of hypercalcemia, serum ACE, hypercalciuria, lupus pernio, erythema nodosum, ocular or other extrapulmonary organ involvement at initial admission and during their follow-up. Neurosarcoidosis was diagnosed by neurologic consultation or by the presence of a central nervous system lesion identified by CT [Computed Tomography (CT)] or MRI (Magnetic Resonance Imaging (MRI)].

Epidemiological, clinical, laboratory, radiologic, histopathologic and prognostic manifestations were acquired from the patient records. Bronchoscopy was carried out under local anesthesia using lidocaine while midazolam was used if indicated. Six bronchial biopsies were taken from each patient if the bronchial mucosa was abnormal. In case of a normal mucosa eight to ten biopsies from different sites, main and secondary carenas of both lungs were taken. Extrapulmonary organ sarcoidosis was classified into two groups as LOI [Limited Extrapulmonary Organ Involvement (LOI)] if less than three organs were involved and as EOI [Extensive Extrapulmonary Organ Involvement (EOI)] when three or more organs were encompassed. Endobronchial disease was designated as LEI [Limited Endobronchial Involvement (LEI)] in the presence of one positive bronchoscopic biopsy sample and as DEI [Diffuse Endobronchial Involvement (DEI)] if two or more biopsy samples were positive for non-calcified granulomatous inflammation.

During follow-up 96 patients were commenced on steroid treatment, 32 patients were given azathioprine and 18 patients were treated with methotrexate. Blood count and serum biochemistry analysis were conducted during the follow-up. FEV_1, FVC, TLC and DLCO/VA were carried out every six months. All patients were monitored every three to six months according to the clinical manifestations and the clinical course of the patient. The mean follow-up period was 138.6 ± 24.8 months. Progressive persistent sarcoidosis was determined if the clinical course worsened in regard to the pulmonary or the systemic symptoms, serious pulmonary function impairment, extrapulmonary organ involvement and the development of significant radiologic findings. Sarcoidosis patients usually have remission within two to five years after the initial diagnosis [10-15] and patients who had manifestations of persistent disease five years following the initial diagnosis are classified as chronic persistent disease. Refractory sarcoidosis lasting more than two years from the initial diagnosis significantly reduces the probability of spontaneous resolution [16-19]. In our study, patients with a stable course or negligible symptoms or trivial laboratory findings five years after the initial admission were approved of a benign disease course.

The patients were classified into two main groups as having normal and abnormal PFTs or DLCO/VA percentage results according to the predicted values in regard to age, height and gender. The patients were divided into four groups for prognostic evaluation. Detoriation of PFT or DLCO/VA, worsening of radiologic findings, existence of hypercalcemia or hypercalciuria, higher than normal ACE levels, systemic involvement such as ocular, cardiac and neurologic disease indicated chronic persistent disease. The classification for prognostic assessment was done by collaborating all the clinical manifestations, laboratory, radiologic findings, pulmonary function test and DLCO/VA values. Patients were also evaluated for the development of hypercalcemia, hypercalciuria, serum ACE, detoriation of pulmonary tests, DLCO/VA or radiologic findings, lupus pernio, erythema nodosum and ocular or any other extrapulmonary organ involvement during their follow-up. Group I included stabile asymptomatic patients with normal laboratory findings. Group II patients had mild symptoms or mildly impaired laboratory results. Group III consisted of patients with moderate symptoms or with moderate laboratory disorders. Group IV included patients with severe deterioration in the clinical and the laboratory manifestations with a chronic persistent disease course. Data variables were embodied as mean ± standard deviation. Statistical differences between the two groups were evaluated in regard to prognosis, pulmonary function test values, DLCO/VA, limited or extensive extrapulmonary organ sarcoidosis and limited or diffuse endobronchial involvement. The χ^2 test was performed for categorical variables as appropriate. Logistic regression was used to determine the effect of age, gender, and splenic

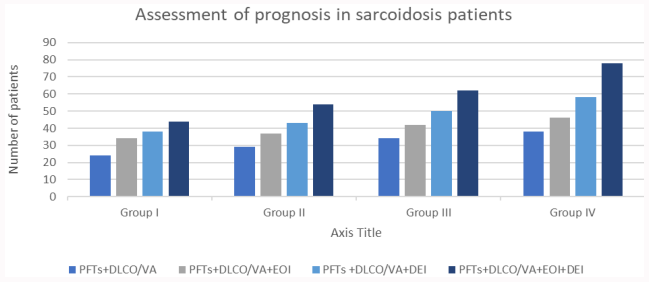

Figure 1: Prognostic evaluation of sarcoidosis patients in regard to PFTs, DLCO/VA, extrapulmonary organ and endobronchial disease involvement.
PFTs [Pulmonary Function Tests (PFTs)], DLCO/VA [Diffusion Capacity/ alveolar Volume (DLCO/VA)],
EOI [Extensive Extrapulmonary Organ Involvement (EOI)]. DEI [Diffuse Endobronchial Involvement (DEI)]

Table 1: Dermographic and clinical characteristics of the patients.

Demographics	**p value**
Total number of patients	194
Age (years)	40.2 ± 14.6 ‹ 0.18
Gender	‹ 0.21
Female patients	104 (53.6%) ‹ 0.24
Male patients	90 (46.4%) ‹ 0.27
Radiologic stage	
Stage 0	22 (11.3%)
Stage I	80 (41.2%)
Stage II	46 (23.7%)
Stage III	34 (17.5%)
Stage IV	12 (6.2%)
Pulmonary function and DLCO/VA (percentage values according to the predicted)	
FEV_1, % predicted	71.6 ± 14.8 ‹ 0.16
FVC, % predicted	74.2 ± 15.6 ‹ 0.10
TLC, % predicted	81.6 ± 17.4 ‹ 0.11
DLCO/VA, % predicted	80.4 ± 10.2 ‹ 0.08
Laboratory	
Serum Ca, mg/dL	8.46 ± 2.6 ‹ 0.18
Urinary Ca, mg/day	268.4 ± 26.8 ‹ 0.14
Serum ACE, IU/L	56.2 ± 18.6 ‹ 0.09

Data are presented as mean ± SD or %. A p value less than 0.05 is significant

disease on prognosis. Krukal-Wallis test and Bonferroni corrected two ways Mann-Whitney test were done to compare group differences. Student's t-test was done to compare the serum ACE, serum and urinary calcium discrepancies between the two groups. Pearson correlation test was performed to appraise the association between two variables. Statistical analysis was evaluated using software (SPSS 22.0 version). A p value less than 0.05 was accepted as the threshold for statistical significance.

Results

A total of 194 patients (104 female, 53.6%) with a mean age of 40.2 ± 14.6 years were evaluated in the study. Table 1 depicts the dermographic distribution and the clinical findings of the entire cohort. Tuberculin skin test was negative in 152 (78.3%) patients. Serum ACE, serum and urine calcium was elevated in 59.7% (116/194), 13.9% (27/194) and 26.8% (52/194) of the patients. Stage distribution, percentage of the pulmonary function test results and DLCO/VA values according to the predicted are shown in Table 1. FOB revealed visible mucosal abnormal findings associated with sarcoidosis in 102 (52.6%) patients while a normal mucosal appearance was observed in the remaining. The most frequent bronhoscopic appearance was miliary infiltration (37.4%) followed by nodular (29.6%) and erythematous lesions (25.2%) while there were mixed type of lesions in 23.8% of the patients. None of the subjects had a complication associated with the bronchoscopic interventions. Culture of bronchoalveolar lavage for bacteria, mycobacteria and fungus was negative in all of the patients. Diagnostic histopathologic tissue was obtained by FOB in 96%, by skin biopsy in 30.2%, *via* mediastinoscopy in 18% and by various organ biopsies in 32% of the patients. Non-calcified granulomas were detected from the endobronchial biopsy samples in 52 (26.8%) patients with a normal mucosal appearance.

Logistic regression with Krukal-Wallis test and Bonferronni corrected two ways Mann-Whitney test revealed no statistical difference of age and gender on prognosis. Serum ACE, serum and urinary calcium values were not distinct ($p<0.09$, $p<0.16$ and $p<0.11$) (Table 1) with respect to the prognostic outcome. The decreased FEV_1, FVC, TLC and DLCO/VA values alone were not statistically significant (r: 0.18, $p<0.12$; r: 0.24, $p<0.16$; $p<0.14$, r: 0.19 and r: 0.21, $p<0.08$) in regard to prognosis. The incidence of decreased TLC and DLCO/VA values were lowest in stage 0 and stage I patients. These values were almost within normal limits in stage 0orstage I patients but revealed an a clinically noteworthy significance for low values in regard to ascending stage but their statistical significance was low (r: 018, $p<0.082$; r: 024, $p<0.076$). They exhibited an increasing trend for decreased values in regard to stage and were most common in stage II, III or stage IV patients but did not reach statistically appreciable levels but their clinical significance was considerable. High serum ACE, hypercalcemia and hypercalcuria were found in 78 (78/194; 40.2%), 32 (32/194; 16.4%) and 58 (58/194; 29.8%) of the patients, respectively. Limited extrapulmonary organ involvement was identified in 82 patients (82/194; 42.2%) while extensive organ sarcoidosis was observed in 48 subjects (48/194; 24.7%). Limited endobronchial involvement was found in 96 (96/194; 49.4%) while diffuse endobronchial sarcoidosis was identified in 90 (90/194; 46.3%) patients.

Prevalence of persistent chronic sarcoidosis and poor prognosis were significantly higher ($p<0.01$) in patients with low TLC and DLCO/VA values who manifested diffuse endobronchial and extensive extrapulmonary organ involvement (Figure 1) revealing a significant correlation (r: 0.96, $p<0.01$) with these parameters with a high sensitivity and specificity (84.2%, $p<0.01$; 78.6%, $p<0.01$) for chronic disease. Logistic regression analysis revealed a 1.42 times worse prognosis in these patients. PFT and DLCO showed a poor correlation with sarcoidosis prognosis if evaluated on their own but when appraised with endobronchial and extrapulmonary organ involvement, the correlation with prognosis reached to noteworthy and statistically significant levels. PFT and DLCO values showed a weak correlation with sarcoidosis prognosis (r: 0.24; $p<0.01$) when evaluated on their own.

Discussion

Sarcoidosis is chronic disease of unknown origin characterized by the presence of granulomas in various organs, especially the lung. PFTs and chest radiology are the initial tests to evaluate pulmonary

sarcoidosis. Unfortunately, PFTs are not a reliable means for detecting the presence of pulmonary sarcoidosis and the majority of sarcoidosis patients will have normal PFTs but may also show a restrictive or an obstructive pattern [10-12]. These tests neither provide an accurate estimate of the extent of parenchymal disease nor provide an objective verification for prognosis [13-16]. The most frequent PFT abnormality is a reduced diffusing capacity that may be relevant to parenchymal involvement or to the presence of pulmonary hypertension. Presence of statistically significant differences in all PFT parameters among the patient groups with different radiographic stages of sarcoidosis has been shown [11,12,14]. Prognostic consequences as well as the diagnostic significance are considered the hallmark of the laboratory tests an in terms of sarcoidosis. PFTs are only a piece of the puzzle for diagnosing pulmonary sarcoidosis while a consistent clinical presentation, imaging and biopsy are required for disease identification [16]. The results of our study reveal PFTs performed as the initial part of the evaluation may provide useful data for estimating the prognostic outcome of sarcoidosis patients if collaborated with endobronchial disease and extrapulmonary organ involvement. PFTs and DLCO/VA have no statistical significance by themselves when evaluated in terms of prognosis and their correlation with disease course is poor and the prognostic significance of serial PFT benchmark is low. When the pulmonary function tests are evaluated along with endobronchial and extrapulmonary organ involvement status they gain a high statistical prominence in terms of prognostic assessment.

However, pulmonary function testing may show normal results even when anatomic changes documented by imaging studies are severe. In one study, only 14.6% of consecutive newly diagnosed sarcoid patients had restriction or mixed restriction and obstruction at presentation. Obstruction was noted in 9.7% of patients, with 47.9% having increased RV/TLC ratio consistent with air trapping and some element of obstruction. This mild obstruction was prevalent from early stages of the disease with the tendency to coexist with restriction as the disease advanced [13,16]. Although, changes in FVC over time only partially correlate with HRCT findings, a combined analysis with DLCO is likely more accurate for assessing disease evolution. The DLCO was reduced in approximately 70% of the patients [14]. Pulmonary function testing allows the clinician to assess changes in the disease course of the individual patient through sequential measurements [10] but their diagnostic and prognostic sensitivity remains low and unpredictable as the results of our study clearly indicate.

There are some limitations of our study. The sample size may be considered small. Larger population sizes are usually needed for epidemiologic and prognostic studies. Second, the patient compliance with the pulmonary function tests and DLCO/VA may be the vulnerable point for our study results. But the pulmonary function tests were repeated at least three times until two FEV_1 values within 5% or 100 ml of the best was obtained. Consequently, patient compliance a negligible relevance while patients who were unable to perform the pulmonary function tests were excluded from the study. Therefore, probability for the accuracy of the pulmonary function test issues is not a concern for faulty or erroneous results. The depth of the mucosal biopsies may be regarded as inadequate to verify the granulomatous inflammation or non-calcified granulomas. The experience of the bronchoscopists in this field who took part in the study can easily disable such a presumption. As far as the follow-up period is concerned, the minimum time interval was five years for the individual patient which is an optimal duration for a chronic or persistent sarcoidosis to come out that is usually accepted to occur within two years after initial admission.

The evaluation of sarcoidosis patients carries the most crucial aspect in terms of treatment, disease course, patient survival and prognosis. It is well-known that great variations may occur in sarcoidosis patients relevant to presentation, diagnosis, treatment and disease course that may arise in the same or between different individuals. This atypical situation is most likely to occur in terms of prognosis. Although a number of prognostic criteria have been recommended for the assessment of the prognostic outcome, none of these have reached a statistically or a clinically significant endpoint and have remained debatable for an unequivocal or an accurate assessment. Absence of erythema nodosum, presence of lupus pernio, hypercalcemia, hypercalcuria, and three or more extrapulmonary organ sarcoidosis, neurosarcoidosis and cardiac involvement have been reported to be indicators of a severe prognostic outcome in sarcoidosis patients [17-22]. Different clinical manifestations, markers and follow-up criteria have been suggested for the identification of patients that have a predisposition to develop chronic persistent sarcoidosis with variable success rates [23-26]. More recently, Yanardag and Tetikkurt have revealed more significant and precise criteria for the chronic and persistent prognostic outcome of sarcoidosis patients including endobronchial, cutaneous, ocular, splenic and muscle involvement [27-30]. Since multiple mechanisms play a role in the development of sarcoidosis, prognostic evaluation of the disease cannot be attributed to a single factor. As in the development of disease it should be considered that multiple factors may play a role in the prognosis of sarcoidosis. Consequently, for more accurate prognostic estimation the patients should be evaluated accordingly for the treatment options and for the disease outcome. Our findings reveal that PFTs and DLCO/VA are only weak prognostic markers on their own. The collaboration of the lung function tests and DLCO/VA along with endobronchial and extrapulmonary organ involvement will yield more accurate and clear consequences for the evaluation of the prognosis in sarcoidosis patients. The above criteria used for predetermining the outcome of sarcoidosis have reached an extremely significant sensitivity and specificity, thus providing a high level of analytical correlation with the disease outcome.

Conclusion

Pulmonary function tests and diffusion capacity may be supportive modalities for the diagnosis and for the assessment of the disease course of the individual patient through sequential measurements in sarcoidosis patients. These tests allow the clinician to evaluate changes in the management of the individual patient. There is a great variability in the follow-up guidelines and no specific criteria exist for PFTs or DLCO/VA in regard to prognostic evaluation of sarcoidosis patients among different centers. The PFTs and DLCO/VA neither clinically nor statistically reveal significant or accurate results for a precise prognostic appraisement. Although changes in FVC or DLCO/VA may correlate with HRCT findings, disease course and prognosis, a combined analysis with endobronchial and extrapulmonary organ involvement appears to be more conclusive for monitoring the disease evolution. The results of our study indicate that the pulmonary function modalities may only provide useful and significant clinical data for the prognosis of sarcoidosis patients if they are collaborated with the endobronchial and extrapulmonary organ involvement. The second crucial conclusion is that the maximum

number of available clinical manifestations of the individual patient should be scrutinized for determining the prognostic outcome of sarcoidosis.

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