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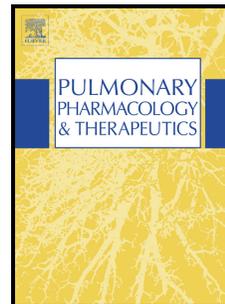
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Title: SYSTEMIC OXIDATIVE STRESS IN PATIENTS WITH PULMONARY SARCOIDOSIS

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ABSTRACT

Background: A local redox imbalance has been reported in pulmonary sarcoidosis. However, so far no study has described a systemic redox imbalance in this context. The aim of the present study was to evaluate the systemic oxidative stress in patients with sarcoidosis and determine its relationship to treatment and indices of disease severity.

Methods: 35 patients with histologically proven pulmonary sarcoidosis and 13 healthy volunteers were included in the study. All patients were studied during a stable phase of their disease. Systemic oxidative stress was quantified in serum with the use of a commercially available spectrophotometric method (D-ROM test) which determines overall oxidative stress, by measuring total hydroperoxides. Oxidative stress was expressed in conventional units, i.e. Carratelli Units (UCarr), where 1UCarr corresponds to 0.8mg/L H₂O₂.

Results: Serum oxidative stress levels were significantly higher in patients with sarcoidosis compared to those of normal subjects (390±25 vs 300±18) UCarr respectively, p=0.04). Patients not receiving systemic corticosteroids had higher levels of oxidative stress compared to steroid-treated patients (461.5±38 vs 315±20, p<0.01) and compared to controls (461.5±38 vs 300±18 UCarr, p<0.01). Oxidative stress did not correlate with diffusion lung capacity (DLCO), partial arterial oxygen tension (PaO₂), MRC dyspnoea scale or chest X-ray stage.

Conclusions: Systemic oxidative stress is increased in patients with stable pulmonary sarcoidosis who do not receive systemic corticosteroids. This finding suggests a sustained oxidative burden even when clinical, functional and radiological criteria indicate disease stability.

KEY WORDS:

Sarcoidosis

Oxidative stress

Corticosteroids

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ABBREVIATION LIST:

EBC: Exhaled breath condensate

IFN- γ : Interferon-gamma

PFTs: Pulmonary function tests

ROMs: Reactive oxygen metabolites

ROS: Reactive oxygen species

TNF- α : Tumor necrosis factor- alpha

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1. INTRODUCTION

Sarcoidosis is a systemic disease of unknown aetiology, characterized by the presence of noncaseating granulomas which affect the lungs in up to 90% of all cases. Although, diagnosis based on a compatible clinical and histological picture is usually straightforward, sarcoidosis still remains an enigmatic disorder[1]. Its diverse manifestations and its variable natural course, which is characterized by episodic recrudescence and remissions, render impossible the prediction of the long-term outcome of any individual patient. Targeting towards better disease understanding and improved patient care, investigators have focused on the identification of biomarkers[2] which would assist diagnosis or disease monitoring and would partly reveal the underlying mechanisms of disease.

The role of oxidative stress has been well documented in several lung diseases, including acute lung injury, asthma, chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis[3-5]. The sequence of events that lead to an increased oxidative burden is considered to commence when a usually unknown triggering factor activates an acute inflammatory response. The recruited inflammatory cells produce and release cytotoxic substances, such as reactive oxygen species (ROS), which perpetuate a vicious circle of amplified tissue destruction and cytotoxic mediator generation.

Oxidative stress has also been implicated in the pathogenesis of sarcoidosis. Although no study has yet described a systemic redox imbalance in this context, several investigators have demonstrated that alveolar macrophages isolated from the bronchoalveolar lavage (BAL) of patients with sarcoidosis are locally activated to produce oxygen radicals in vitro[6, 7]. This enhanced oxidative activity is also expressed in vivo as inferred by the elevation of 8-isoprostane, an oxidative product

of arachidonic acid, in BAL[8] and exhaled breath condensate (EBC)[9] of sarcoidosis patients. The aim of the present study was to evaluate the systemic levels of oxidative stress in the serum of patients with sarcoidosis using a commercially available and easy to perform assay, and to explore the relationship between these levels, the severity of dyspnoea and the impairment of lung function in such patients. In addition, the present study also assessed whether oxidative stress levels are influenced by treatment with corticosteroids.

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2. MATERIAL AND METHODS

2.1 Study population

Patients with histologically proven pulmonary sarcoidosis were considered for entry into the study if they presented during a stable phase of their disease. Patients with active sarcoidosis, those receiving corticosteroids for less than six months, smokers and subjects with co-morbidities, a respiratory tract infection during the past two months, allergies or asthma were excluded. Healthy volunteers, matched in age and gender with the patients, were used as controls. The study protocol was approved by the local ethics committee and all participants gave verbal and written informed consent to participate in the study.

2.2 Disease assessment

Sarcoidosis activity was assessed as previously described in accordance to published guidelines[1, 9]. A detailed medical history, symptoms (MRC dyspnea scale) and clinical examination findings were recorded. Arterial blood gas, complete blood count, liver and renal function tests, serum calcium and 24-hour urine calcium measurements were also carried out.

Pulmonary function tests (PFTs) were performed within 7-days from the measurement day and included assessment of FEV₁, FVC, FEV₁/FVC ratio, TLC, RV and DLCO. Static volumes and DLCO were measured with the helium dilution method and the single breathholding helium dilution method respectively, using the Master Screen apparatus (Erich Jaeger GmbH, Wuerzburg, Germany). Current PFTs were compared with those conducted 3 months earlier. A decline in lung volumes of $\geq 10\%$ or $\geq 200\text{ml}$ and in DLCO of $\geq 15\%$ or $\geq 3\text{ml}/\text{min}/\text{mmHg}$ was considered to reveal sarcoidosis activity[9].

High resolution computed tomography (HRCT) scans were performed using either a Somatom HiQ or a Somatom Plus scanner (Siemens, Erlanger, Germany) and were reviewed for signs of radiological deterioration. Scans were performed with 1-1.5mm section thickness and a 1-2s scanning time during breath holding at end inspiration within 3 months from the serum sampling day.

2.3 Measurement of oxidative stress

At the time of subject evaluation blood samples were collected and centrifuged at 1500xg for 10min at 4°C. Oxidative stress was measured immediately after serum collection with the use of a commercially available method (D-ROM test; Diacron, Grosseto, Italy) as previously described[5, 10-12] by an investigator (T.K.) who was unaware of the subjects' clinical features.

The D-ROM test is a spectrophotometric method that measures the derivatives of reactive oxygen metabolites (ROMs) and assesses overall oxidative stress, by measuring total hydroperoxides. The latter are generated by the action of oxidative stress on lipids, peptides and aminoacids and their amount reflects the total oxidative burden. Total hydroperoxides are detected spectrophotometrically and oxidative stress is expressed in conventional units (Carratelli Units, where 1UCarr corresponds to 0.8mg/L H₂O₂). The normal values of the test are between 250 and 300 UCarr Carratelli Units). Values outside this range are considered indicative of an alteration in the equilibrium between prooxidant and antioxidant capability of subjects. Values >300 UCarr indicate a condition of oxidative stress.

3. STATISTICAL ANALYSIS

Analysis was performed and graphs were drawn with the use of SPSS 15.0 for Windows. Data's normality of distribution was examined with the use of the Kolmogorov-Smirnov test. As D-ROMS test was normally distributed, comparison of the two main groups of subjects (normal subjects and sarcoidosis patients) was assessed with the unpaired *t* test, whether One way analysis of variance (ANOVA) was used to compare multiple groups of subjects and Bonferroni's correction was applied to compare selected pairs of groups. As the distribution of dyspnea (MRC scale), PFTs, PO₂ or chest X-ray stage was skewed, Mann-Witney U test was used for the comparison of the two main groups of subjects (normal subjects and sarcoidosis patients) and Kruskal-Wallis test was used to compare multiple groups of subjects. Spearman's correlation coefficient was utilized to determine the relationship between different variables. Data were presented as mean±SEM and statistical significance was defined as a *p*-value of less than 0.05.

4. RESULTS

In this clinical study we investigated 35 patients with histologically proven pulmonary sarcoidosis during a stable phase of their disease and 13 healthy volunteers that served as controls. Disease duration prior to the study was 2 ± 1 years (mean \pm SD). The clinical characteristics of the 48 subjects who participated in this study are summarized in Table 1. The study populations did not differ significantly in terms of sex and age.

All patients reported stability of their symptoms during the last 6 months and physical examination did not indicate disease activity. Complete blood count and biochemical tests were also within normal range. Additionally, a comparative study of the current PFTs and those conducted 3 months earlier did not reveal a significant decline of lung volumes and DLCO. Finally, chest radiographies (CXR) and HRCT scans of the chest revealed no signs of radiological deterioration.

Eighteen patients with sarcoidosis had reached disease stability state while receiving oral corticosteroids for at least six months, 12 were steroid naïve and 5 had not received systemic corticosteroids for at least six months. The original decision to administer systemic corticosteroids was in accordance to the ATS/ERS/WASOG criteria: 12 patients received therapy due to progressive symptomatic pulmonary disease, 4 due to asymptomatic pulmonary disease with persistent infiltrates, 1 with neurological disease and 1 due to eye disease not responding to topical therapy (Table 2).

Sarcoidosis patients were divided into two groups according to the use of corticosteroids. The first group, steroid-treated patients, consisted of 18 members and the second group, patients not receiving systemic corticosteroids, consisted of 17 members. The two groups did not differ significantly according to age, gender, radiological stage, MRC dyspnoea scale, PFTs and disease duration (Table 1).

Oxidative stress levels were significantly higher in patients with sarcoidosis compared to those of normal subjects (390 ± 25 vs 300 ± 18 UCarr respectively, $p=0.04$) (Figure 1). Patients not receiving systemic corticosteroids had higher oxidative stress compared to steroid-treated patients (461.5 ± 38 vs 315 ± 20 , $p<0.01$) and compared to controls (544 ± 171.6 vs 300 ± 18 UCarr, $p<0.01$) (Figure 2). Oxidative stress levels in patients receiving corticosteroids did not differ significantly compared to controls (315 ± 20 vs 300 ± 18 UCarr, $p>0.05$). Levels of oxidative stress did not correlate significantly with dyspnea (MRC scale), PFTs, PO_2 or chest X-ray stage.

5. DISCUSSION

In the current study we have demonstrated that patients with sarcoidosis, assessed during a stable phase of their disease, have higher systemic oxidative stress levels compared to controls, whereas patients receiving systemic corticosteroids have systemic oxidative stress levels similar to that of normal subjects. According to our knowledge, this is the first study to demonstrate a systemic Redox imbalance in the context of sarcoidosis and to provide evidence of a sustained oxidative burden during clinical stability.

As already mentioned, previously conducted studies assessing oxidative stress in sarcoidosis have focused exclusively on the local redox imbalance observed both in vitro and in vivo. Several investigators have demonstrated that alveolar macrophages isolated from the BAL of sarcoidosis patients possess an enhanced capacity to metabolize oxygen and to produce hydrogen peroxide and superoxide anions, especially under the influence of activating substances[6, 13-16]. In accordance to these in vitro observed phenomena, the EBC of sarcoidosis patients has elevated levels of 8-isoprostane[8, 9], whereas in the present study a systemic redox imbalance was also observed.

Although the aetiology of sarcoidosis remains uncertain[17], extensively conducted research has revealed several of the histopathologic and immunopathogenic events which occur during the development of noncaseating granulomas and might interpret the aforementioned redox imbalance[18, 19]. Granuloma formation is considered to implicate the selective accumulation of CD4+ T cells and macrophages which release cytokines, such as interleukin-2 (IL-2), interferon-gamma (IFN- γ) and tumor necrosis factor alpha (TNF- α)[20]. Previous studies focusing on the interaction between inflammation and oxidative stress

signalling cascades have demonstrated that the inflammatory changes induced by the accumulation of cytokines create a microenvironment which affects redox-related pathways, gene expression and ultimately cell survival[13, 21, 22]. Those local events might also cause systemic alterations accounting for the elevation of systemic oxidative stress.

Sarcoidosis is characterized by a wide clinical variability, as far as localization and severity of clinical manifestations are concerned, especially during disease activity. In the current study we assessed disease activity according to published guidelines[1] and included only stable sarcoidosis patients in an attempt to obtain a homogenous population. In the study of Montuschi and colleagues, it was demonstrated that sarcoidosis patients, irrelative of disease activity, have elevated EBC 8-isoprostane levels as compared to controls[8], whereas Psathakis and co-workers reported that increased 8-isoprostane was observed only during disease activity[9]. In the present study we have demonstrated that clinically stable sarcoidosis is characterized by a systemic redox imbalance. This finding implies that the underlying pathophysiological events that occur during sarcoidosis persist even when clinical, functional and radiological criteria indicate disease stability.

Although in a previous study, focusing on idiopathic pulmonary fibrosis, we have shown that systemic oxidative burden correlated with functional parameters expressing disease severity[5], in the present study oxidative stress levels did not correlate with clinical parameters, such as dyspnea, PFTs, PO₂ and chest X-ray stage. The latter is in accordance with previous publications reporting that EBC 8-isoprostane levels in sarcoidosis did not correlate significantly with PFTs or radiographic changes[8, 9]. This inability to demonstrate a statistically significant correlation could perhaps be attributed to the fact that oxidative stress provides an

insight into the ongoing (during sample collection) pathophysiological status whereas clinical parameters reflect the result of previously occurring processes[9]. An alternative explanation to that lack of that significant correlation could be the fact that systemic oxidative stress in sarcoidosis might result from systemic rather than pulmonary disease activity unlike IPF.

An additional noteworthy observation is that patients receiving systemic corticosteroids have oxidative stress levels similar to that of controls. Although lack of serial measurements (before and after therapy administration) limits definite conclusions this finding suggests a reduction of oxidative stress under the influence of systemic corticosteroids. This is in accordance to the already known immunomodulatory role of corticosteroids and their ability to suppress inflammation by activating anti-inflammatory genes or by disabling inflammatory genes[23]. The complex interactions between inflammation and redox-related pathways which have already been described might also explain the lower systemic oxidative stress in patients receiving corticosteroids.

The current study is only a preliminary step in investigating the role of systemic oxidative stress in sarcoidosis and in delineating its function as a novel biomarker for disease monitoring. Although the D-ROM test is a simple, economic assay, with an excellent repeatability and reproducibility[5], that can be easily performed in everyday clinical practice, the role of systemic oxidative stress as a biomarker in the context of sarcoidosis can only be suggested. The small number of subjects and the lack of measurements during disease activity or before and after the administration of corticosteroids are some of the study's limitations that need to be acknowledged and addressed.

6. CONCLUSIONS

Patients with stable sarcoidosis that do not receive corticosteroids have elevated systemic oxidative stress levels. This finding advocates towards a potential key role of oxidative stress in the pathogenesis of the disease and implies that the underlying pathophysiological events that occur during the course of sarcoidosis persist even when clinical, functional and radiological criteria indicate disease stability. Although so far there is no available biomarker sensitive enough to monitor sarcoidosis activity and remission, future studies that will target towards redox imbalance might provide further support on its role as a biomarker in this context, whereas therapeutic approaches targeting towards its attenuation may provide novel perspectives in the management of sarcoidosis.

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FIGURE LEGENDS

Figure 1: Comparison of serum oxidative stress between sarcoidosis patients and controls. The mean values are indicated by the horizontal bars.

Figure 2: Comparison of serum oxidative stress between sarcoidosis patients not receiving systemic corticosteroids, patients receiving systemic corticosteroids and controls. The mean values are indicated by the horizontal bars.

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TABLES**Table 1:** Characteristics of study subjects.

Variables	Sarcoidosis patients	Patients receiving systemic corticosteroids	Patients not receiving systemic corticosteroids	Control subjects
Subjects, No	35	18	17	13
Gender, Male:Female No	9:26	5:13	4:13	3:10
Age, yrs	57.6±10.0	54.4±8.7	60.9±10.6	50±16.5
Radiographic staging, 0:I:II:III:IV	0:14:7:14:0	0:6:5:7:0	0:8:2:7:0	NA
PaO ₂ , mmHg	80±1.7	81±3	79±2	82.2±3.1
PFTs, % predicted				
• FEV ₁	87.7±2.5	87±4	88±3	90.1±5.0
• FVC	92±1.5	91±2	92.7±2.3	91.3±3.4
• DLCO	82.3±2*	80±2.5*	84±3	91.3±3.4

Data are presented as mean±SEM, unless otherwise indicated; * signifies p<0.05 as compared to controls. No statistically significant differences existed among the subgroups of patients with sarcoidosis.

Abbreviations: PaO₂: partial arterial oxygen tension; PFTs: pulmonary function tests; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; DLco: diffusion lung capacity (single breath); NA: not applicable.

Table 2: ERS/ATS/WASOG criteria for considering corticosteroid treatment in sarcoidosis

ERS/ATS/WASOG criteria	No of patients fulfilling a specific criterion:
• Progressive symptomatic pulmonary disease	12
• Cardiac disease	0
• Asymptomatic pulmonary disease with persistent infiltrates or progressive loss of lung function	4
• Neurological disease	1
• Eye disease not responding to topical therapy	1
• Symptomatic hypercalcemia	0
• Other symptomatic/progressive extrapulmonary disease	0

Figure 1

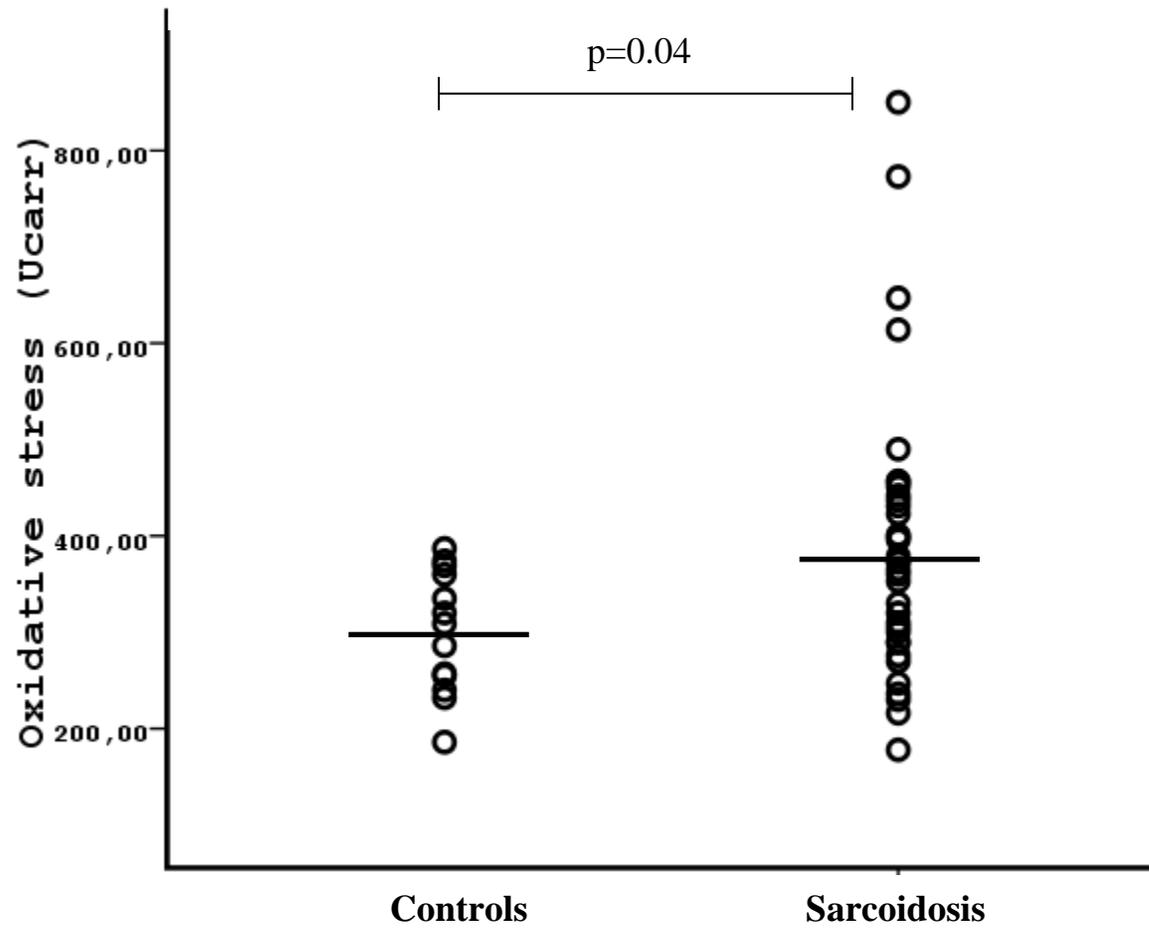


Figure 2

