



Coexistence between fatigue and oxidative stress – total antioxidative status (TAS) in patients with sarcoidosis

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Abstract

BACKGROUND: The aim of this study is to elucidate a link, if any, between total antioxidant status (TAS) and fatigue in sarcoidosis.

METHODS: 69 sarcoidosis patients were analyzed. (53female/16male). 39 patients had chronic form of sarcoidosis. Fatigue was measured using Fatigue Assessment Scale (FAS) and total antioxidative status (TAS) level as a measure of total non-enzymatic power, was measured by Erel method. (In one of our previous studies in 213 sarcoidosis patients and 187 healthy adults we found the TAS level was significantly higher in sarcoidosis patients. [1,46 (1.39-1.56) vs. 0.84 (0.73-0.9) mmol/l, P<0,001]¹.

To assess the link between total FAS score and total TAS, the curve estimation procedure was used. In order to find the discrimination, sensitivity and specificity between the groups ((FAS≥22) and TAS values the ROC curve procedure was used. For making the decision on coexistence between high total FAS score and TAS we used the commutation rule and the opposite probabilities. Significance level 0.05. Statistical analyses were done using SPSS version 18, Chicago, Illinois. **RESULTS:** Mean total FAS score in the analyzed group was 27.06±9.67 and mean TAS was 1.45±0.20mmol/L. The curve estimation procedure resulted in exponential curve (R square=0.96) with the link between total FAS score and TAS. (FAS=e^{2.177xTAS}). Using the logarithm transformation the equivalent value for FAS =22 is TAS = 1.40mmol/L. 33 patients in the analyzed group had (FAS≥22) and (TAS≥1.40mmol/L). The sensitivity for FAS cut off 22.5 was 97% and specificity 65% while the sensitivity for TAS cut point 1.40mmol/l was 94% and specificity 64%. Applying the opposite probability rule and the commutation we concluded that the coexistence of high values of FAS score and high values of TAS score among patients with sarcoidosis had sensitivity over 99% and specificity of 87.4%. **CONCLUSION:** High total FAS score (FAS≥22) in sarcoidosis patients in more than 99% coexists with high total antioxidant status (TAS≥1.40) suggesting the fact that better control of total antioxidative status (TAS) level, as a measure of total non-enzymatic power, may result in the better control of fatigue.

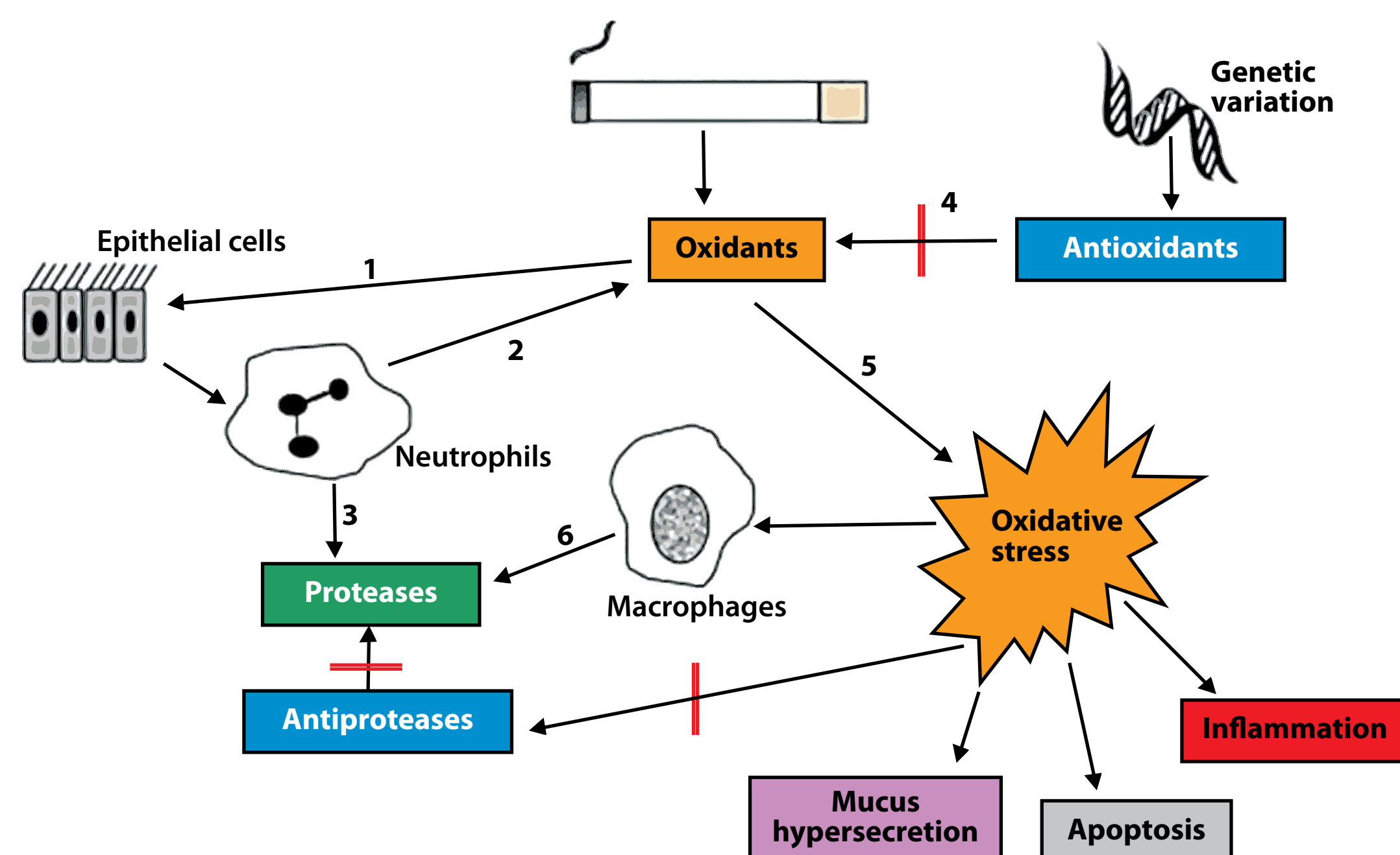
Introduction

Sarcoidosis is an antigen-driven, multisystem, granulomatous disorder of unknown etiology. It is possible that reactive oxygen species (ROS) play a pivotal role in the etiology of granulomatous inflammation -sarcoidosis. Increased levels of ROS are also capable of initiating and mediating inflammation in the lung and thus causing the progression of the disease too.

Fatigue is a prominent feature of sarcoidosis. The condition characterized by debilitating sensation of weakness and extortion and other nonspecific symptoms. The pathophysiology of fatigue continues to remain elusive, although recent evidence suggests excessive free radical generation may be involved.

Related to these observations, antioxidant supplementation might be beneficial in the treatment of fatigue in sarcoidosis.

The aim of this study was to elucidate a link, if any, between total antioxidant status (TAS) and fatigue in sarcoidosis.



Patients & Methods

69 biopsy positive sarcoidosis patients were enrolled in this study. 30 patients had acute sarcoidosis (disease duration less than 2 years) while 39 patients had chronic sarcoidosis, (disease duration more than 2 years).

Extra pulmonary disease had 55 patients, 14 patients had only pulmonary involvement. All patients voluntarily cooperated in completing the study questionnaire (FAS), before the blood samples were obtained for oxidative stress analyses.

Table 1. Descriptive statistics: TAS and FAS total scores

	Gender	Mean	SD	N
FAS total score	male	21.9375	9.79434	16
	female	28.6038	9.66823	53
	Total	27.0580	10.03360	69
TAS (mmol/l)	male	1.5488	.20992	16
	female	1.4226	.19539	53
	Total	1.4519	.20442	69

The FAS is a fatigue questionnaire consisting of 10 items: five questions reflecting physical fatigue and five questions for mental fatigue. The response scale is a 5-point scale (1 = never to 5 = always). Scores on the FAS can range from 10 to 50. Cut off 22. Mean FAS score in our patients group was 27.06±9.67.

Total antioxidative status (TAS) level as a measure of total non-enzymatic power, was measured by Erel method. Mean TAS value in the same group of sarcoidosis patients was 1.45±0.20mmol/L.

Previous study of oxidative stress status in our sarcoidosis patients vs. healthy controls

Oxidative-stress (analyzed in this study)	Sarcoidosis (Number of patients)	Healthy Controls (Number)	P value
	213	187	
Malondialdehyde (MDA)	1.16 µmmol/L (1.02-1.40)	1.07 µmmol/L (0.82-1.25)	P< 0.05
Total oxidant status (TOS)	17.6 µmmol/L (11.2-18.9)	2.13 µmmol/L (1.06-4.18)	P<0.001
Antioxidative status			
Sulphydryl groups (SH)	0.44 mmol/L (0.33-0.54)	0.51 mmol/L (0.47-0.54)	P<0.001
Superoxid-dismutase (SOD)	13 U/L (9-19)	111U/L (100-143)	P<0.001
Total antioxidative status (TAS)	1.46 mmol/L (1.39-1.56) ↑	0.84 mmol/L (0.73-0.9)	P<0.001

OXIDATIVE STRESS STATUS IN SARCOIDOSIS PATIENTS AND CORRELATION WITH CLINICAL PARAMETERS
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Results

The curve estimation procedure revealed significant exponential relation between FAS total score and TAS (R square=0.96), FAS=e^{2.177xTAS} (Table 2 and Figure 1)

Table 2. Exponential prediction model (Regression coefficient) FAS and TAS

Regression parameters				95% Confidence interval for B		
R square=0.965	B	SE	t	p	Lower bound	Upper bound
TAS (mmol/l)	2.177	.050	43.131	.000	2.079	2.275

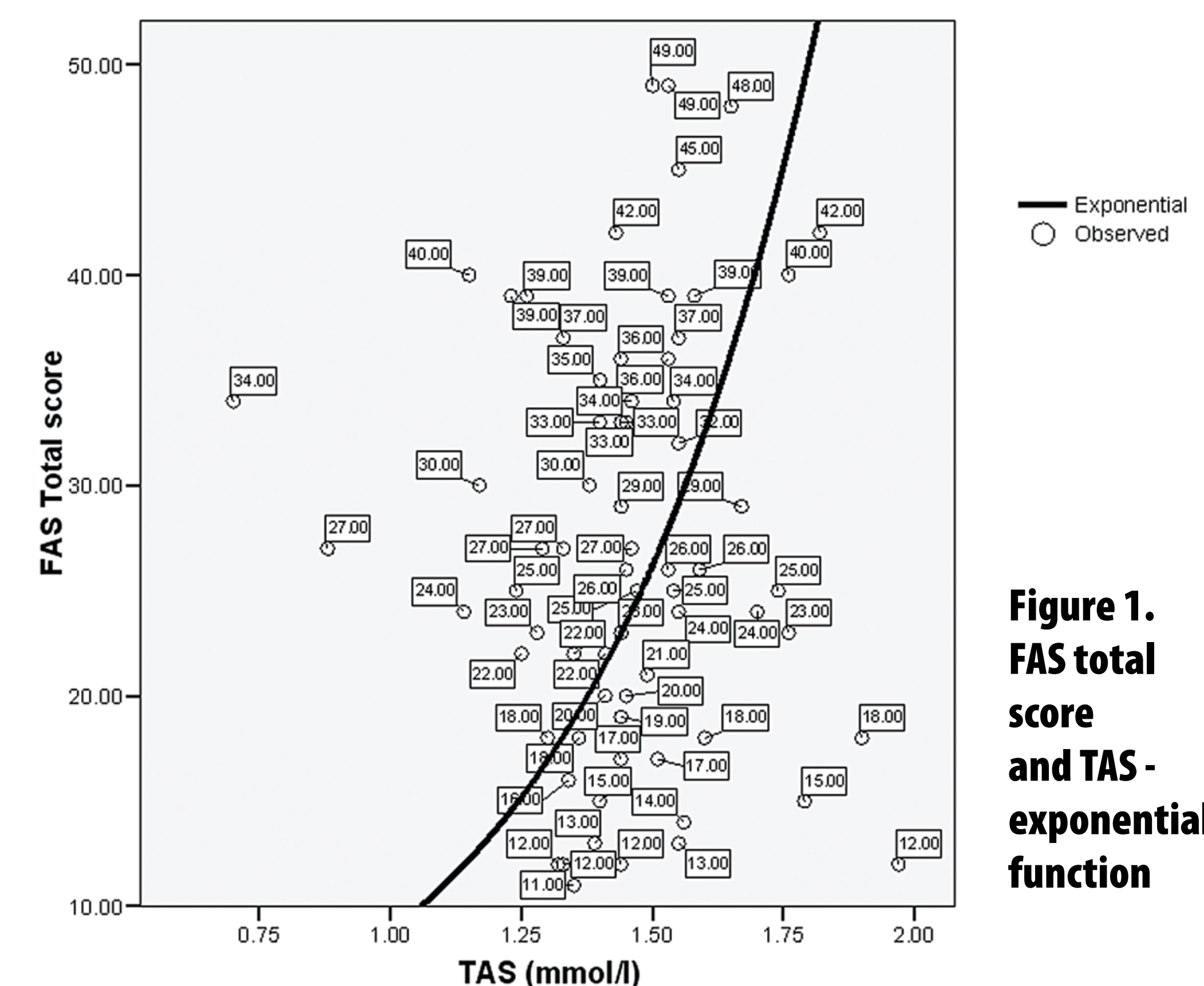


Figure 1. FAS total score and TAS - exponential function

Using the procedure of natural logarithm transformation (FAS =22) the equivalent TAS value was estimated TAS=1.40mmol/L. Thus 33 patients from the analyzed group had FAS≥22 i TAS≥1.40mmol/L. The remaining 36 patients had lower Total FAS score and lower TAS values.

Table 3. Area under the curve: TAS and FAS total score

Variables	Area	SE	p	Asymptotic 95% Confidence Interval	
				lower bound	upper bound
FAS total score	.836	.049	.000	.740	.932
TAS (mmol/l)	.809	.056	.000	.698	.919

Regarding to the former we estimated the area under the ROC curve for FAS total score (area= 0.836, 95%Confidence Interval from 0.74-0.93. TAS area under the curve = 0.84, 95% Confidence Interval from 0.698-0.92. (Table 3 i Figure 2). Sensitivity and specificity (FAS cut off 22) were 97% and 65%, while the sensitivity and specificity values for TAS cut off 1.40 mmol/l were 94% i 64%.

Counting the opposite probability for sensitivity [(1-(1-0.97) x (1-0.94)], we estimated that the coexistence of high Total FAS score ≥ 22 and TAS ≥ 1.40mmol/L was 99%.

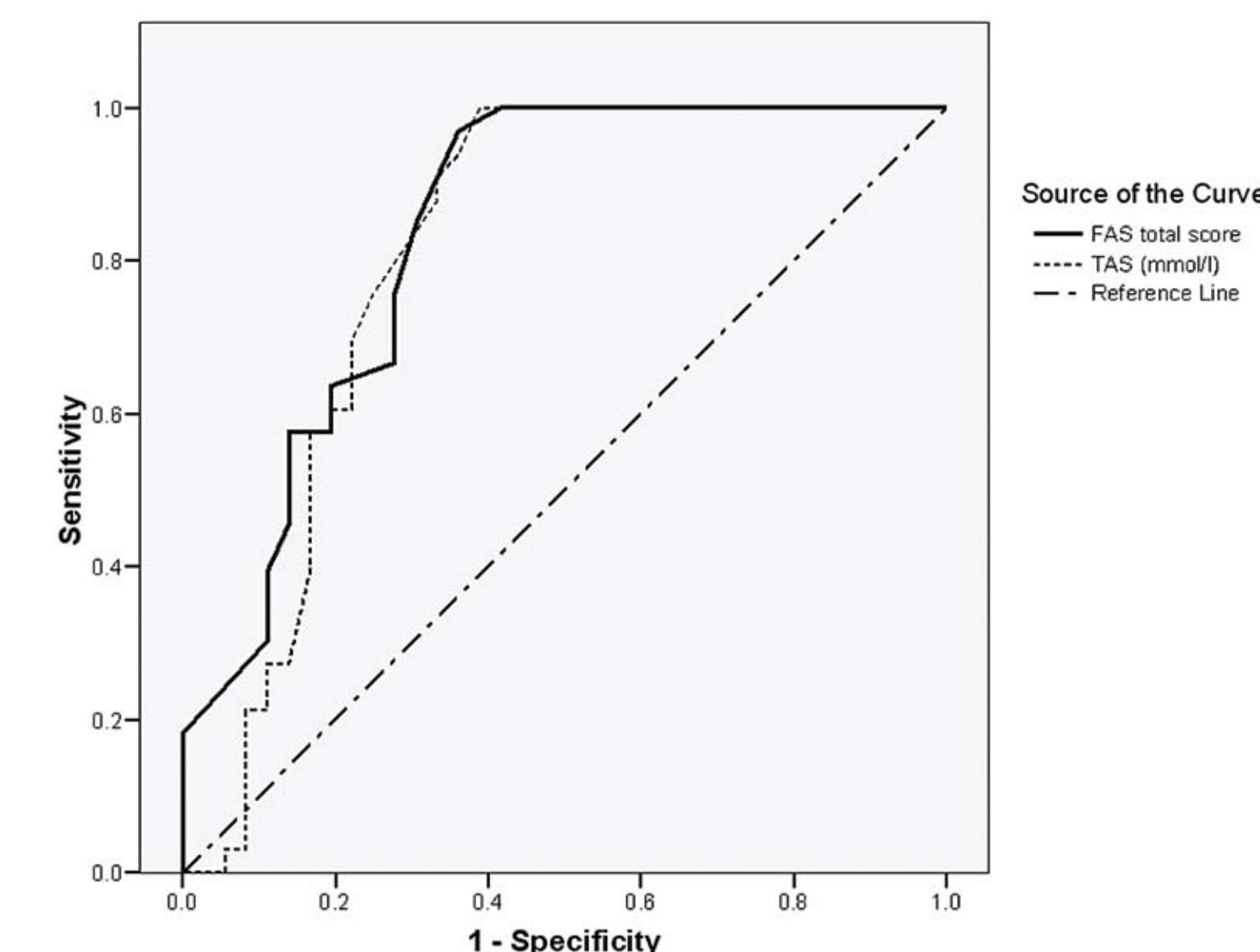


Figure 2. ROC curve for TAS and FAS total score (FAS≥22 and TAS≥1.40 mmol/L)

Statistical methods

The curve estimation procedure was used in order to estimate the correlation between the total FAS score and total antioxidative status (TAS) as a measure of non enzymatic power, compensatory increased in our sarcoidosis patients as we noticed in a previous study.

Statistical analyses were done using SPSS version 18, Chicago, Illinois and MedCalc (trial version) statistical package for medical calculations (ROC curve procedure for FAS and TAS values).

Discussion

Our study revealed that the level of total antioxidative status as a measure of non enzymatic power, might predict the level of fatigue in sarcoidosis patients.

The most interesting fact was that the coexistence of high TAS and fatigue (expressed as total FAS score) was exponential.

Analyzing fatigue in the light of high TAS values, one can expect in 97% of sarcoidosis patients with Total FAS score > 22 the elevation of TAS > 1.40 mmol/l.

Also in 94% of sarcoidosis patients with TAS > 1.40 mmol/l one can expect high Total FAS score > 22.

Conclusion

In 99% of sarcoidosis patients with FAS ≥22 i TAS≥1.4 mmol/l, one can expect the exponential increase of fatigue with the increase of TAS.

Additional antioxidant therapy might have significant role in the treatment of sarcoidosis patients in order to subdue fatigue.