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Diagnostic Values of Clusterin and α-Klotho Levels in Patients with Sarcoidosis

Sarkoidozlu Hastalarda Clusterin ve α-Klotho Düzeylerinin Tanısal Değerleri

Turan Akdag[1],
Celalettin Korkmaz[2],

[1] *Necmettin Erbakan University, Meram Vocational School, Konya, Turkey*
[2] *Necmettin Erbakan University, Meram Faculty of Medicine, Department of Chest Diseases, Konya, Turkey*

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Address correspondence to: Turan Akdag, Necmettin Erbakan University, Meram Vocational School, Konya, Turkey
e-mail: turanakdag570@gmail.com

ORCID
Turan Akdag
https://orcid.org/0000-0003-3175-6751
Celalettin Korkmaz
https://orcid.org/0000-0001-8602-0368

Öz

Amaç: Sarkoidoz, etiyolojisi bilinmeyen ve non-kazeifiye granülomatöz inflamasyon ile karakterize multifaktöriyel bir hastalıktır. Sarkoidoz patogenezi ise inflamasyon ve otoimmün aktivasyon olarak tanımlanır. Bu nedenle sarkoidoz hastalığında plazma clusterin ve α-klotho düzeylerini değerlendirmeyi amaçladık.
Hastalar ve Yöntem: Sarkoidozlu 40 hasta (ortalama yaş: 52,10±12.60 yıl; 12 erkek, 28 kadın) ve 40 sağlıklı gönüllü (ortalama yaş: 37,40±18.20 yıl; 12 erkek, 28 kadın) Kasım 2019-Mart 2020 tarihleri arasında çalışmaya alındı. Her iki gruptan alınan kan örnekleri ile plazma clusterin ve α-klotho düzeyleri enzime bağlı immünosorban testi (ELISA) ile araştırıldı.
Bulgular: Sarkoidozlu hastalarda plazma clusterin düzeyleri (309.73±40.68 ng/ml) sağlıklı gruba (117.86±102.03 ng/ml) kıyasla anlamlı olarak daha yüksekti (p=0.005). α-klotho plazma düzeyleri ise sarkoidoz grubunda 5.34±7.30 ng/ml ve sağlıklı grupta 7.21±9.84 ng/ml olarak belirlendi, minimal bir azalma gözlendi ancak istatistiksel olarak anlamlı bir fark yoktu (p=0.338). Sarkoidozlu hastaların hemoglobin düzeylerinin sağlıklı gruba göre azaldığı belirlendi (12.93±1.02 g/dL'ye karşılık 14.06±1.50 g/dL) (p=0.012).
Sonuç: Sarkoidozun bağımsız olarak yüksek seviyelerde clusterin ile ilişkili olduğu sonucuna varıldı. Plazma clusterin düzeyleri sarkoidoz için potansiyel bir biyobelirteç olabilir. Literatüre göre bu çalışma, sarkoidozda clusterin ve α-klotho' nun plazma seviyeleri için bilgi verilen ilk çalışmadır. Bu konuda daha fazla ve kapsamlı araştırmalara ihtiyaç vardır.

Anahtar Kelimeler: Sarkoidoz, clusterin, α-klotho, inflamasyon, akciğer hastalığı

Abstract

Aim: Sarcoidosis is a multifactorial disease with unknown aetiology and characterized by non-caseous granulomatous inflammation. The pathogenesis of sarcoidosis is defined as inflammation and autoimmune activation. Here, we aimed to evaluate plasma clusterin (CLU) and α-klotho levels in those with sarcoidosis.
Patients and Methods: Forty patients with sarcoidosis (mean age: 52.10±12.60 years; 12 males, 28 females) and 40 healthy volunteers (mean age: 37.40±18.20 years; 12 males, 28 females) between November 2019-March 2020 were enrolled into the study. Blood samples were drawn from both groups, and plasma CLU and α-klotho levels were investigated by enzyme-linked immunosorbent assay (ELISA) technique.
Results: Patients with sarcoidosis had significantly higher plasma CLU levels (309.73±40.68 ng/mL), compared with healthy controls (117.86±102.03 ng/mL) (p=0.005). The plasma levels of α-klotho were measured as 5.34±7.30 in the sarcoidosis patients and 7.21±9.84 ng/mL in the controls. A minimal decrease was observed, but there was no statistically significant difference (p=0.338). The hemoglobin levels of sarcoidosis patients were decreased, when compared with the control group (12.93±1.02 g/dL vs 14.06±1.50 g/dL) (p=0.012).
Conclusion: We concluded that sarcoidosis is associated with high levels of CLU. Plasma CLU may be a potential biomarker of sarcoidosis. Based on literature and to the best of our knowledge, this is the first study to provide insight in the determination of plasma levels of CLU and α-klotho in sarcoidosis. Further and comprehensive investigations are needed to clarify the entity.

Key words: Sarcoidosis, clusterin, α-klotho, inflammation, pulmonary disease

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INTRODUCTION

Sarcoidosis is a multifactorial disease with unknown aetiology and characterized by non-caseous granulomatous inflammation. While affecting all races and both genders, sarcoidosis is usually encountered in young and middle-aged adults (1). Although the most affected areas are mediastinal lymph nodes and lungs, the involvements may be seen in many organs, such as the heart, liver, peripheral lymph nodes, salivary glands, nervous system, musculoskeletal system, hilar lymphadenopathy, eyes and skin (2). The diagnosis of sarcoidosis is performed under the following criteria: a) clinical, laboratory and radiographic findings b) the combination of the histopathological findings that can be displayed in more than one system with the non-caseating epitelioid cell granuloma, c) the exclusion of other causes leading to granulomatous inflammation, and d) the histological analysis of the tissue for the identification of non-caseating granulomas (3).

Although the etiology of sarcoidosis has yet to be elucidated, some factors have recently been proposed, such as oxidative stress, genetic susceptibility, environmental exposure, infections, putative antigens and autoimmune activation (4). An unknown antigen processed by activated macrophages induces an immune response regulated by macrophages and T-cells. These activated cells release different mediators, including cytokines, reactive oxygen species and chemokines, by acting a role in the pathogenesis of sarcoidosis (5). In practice, novel biomarkers have been suggested for the diagnosis of sarcoidosis, but none has been accepted completely yet.

Clusterin (CLU), known previously as apolipoprotein J/ApoJ, is a heterodimeric protein (disulfide-linked) with 75-80 kDa and highly conserved in mammalian tissues (6). The gene of CLU is located on the chromosome 8p21.1 and encodes CLU glycoprotein expressed in nearly all tissues, including brain, testes, liver, pancreas, heart, kidney and lungs (7,8). As a member of the small heat shock protein family, CLU is also a stress-induced molecular chaperone (9). CLU is involved in many physiological processes, such as oxidative stress, lipid transport and membrane remodeling (10). The expressions of CLU are elevated in acute myocardial infarction, inflammation, myocarditis and atherosclerosis (11). Also, CLU has been linked to oxidative stress in both chronic obstructive pulmonary disease (COPD) and asthma (12).

As a transmembrane protein, α-klotho, composed of two parts as the elongation from outside the cell into cytoplasm and upon the membrane surface, consists of 1014 amino acids and weighs about 130 kD. Besides, α-klotho forms the complexes by fibroblast growth factor receptors (FGFR) and serves as a coreceptor for FGFR-23 (13). The gene of α-klotho localized at the 13q12 chromosomal region in humans and composed of five exons and four introns (14). In physiological processes, α-klotho plays a role in maintaining the homeostasis of calcium and phosphate, buffering of elevated reactive oxygen species and the modulation of cell proliferation (15). In addition, α-klotho can suppress oxidative stress and inflammation, so it may reduce oxidative damage in pulmonary epithelia (16).

The aim of the present study was to determine the plasma CLU and α-klotho levels, and to assess the potential role of these biomarkers in the patients with sarcoidosis. In the light of literature and to our knowledge, the plasma levels of CLU and α-klotho have yet to be investigated previously in sarcoidosis patients.

PATIENTS AND METHODS

Eighty participants were enrolled into this cross-sectional study and divided into two groups as the patients and healthy volunteers. The patients' group was constituted from sarcoidosis patients (28 women and 12 men) admitted to the department of pulmonary disease in between November 2019 and March 2020. The control group composed of the healthy volunteers (28 women and 12 men) was selected among the participants with no complaints related to sarcoidosis. The participants between the ages of 18-65 were enrolled into the study. None of the participants were detected to have a metabolic disease before the study. Those with the following criteria were excluded out of the study: Known endocrinopathies, neoplastic disorders, cardiovascular diseases, thyroid disease, pregnancy, diabetes mellitus and hypertension for at least 3 months. The sarcoidosis patients were diagnosed by an experienced clinician, and the cases were also confirmed by lung X-rays and high resolution computed tomography (HRCT). The demographic and clinical measurements were recorded on the same day. Plasma samples were centrifuged within 30 minutes at 3.000 rpm for 15 minutes. The plasma was, then, removed and stored at -80 0C until the assay. The plasma levels of CLU and α-klotho were analyzed by enzyme-linked immunosorbent assay (ELISA) kits. The present study was conducted in accordance to

the declaration of Helsinki, and the study approval was obtained from Necmettin Erbakan University Meram Faculty of Medicine, Non-interventional Clinical Trials Ethics Committee (Decision No: 2019/2083). Written and informed consent statements were obtained from all participants.

The plasma concentrations of CLU were analyzed by human CLU immunoassay kits. While the minimum detectable concentration (sensitivity) was measured as 0.54 ng/mL, the assay range, intra-assay variation and inter-assay variation were detected as 1-300 ng/mL, <8%, and <10%, respectively. The plasma levels of α-klotho were measured by human α-klotho immunoassay kits. The rates of sensitivity, assay range, intra-assay variation and inter-assay variation were also measured as 0.027 ng/mL, 0.05-20 ng/mL, <8% and <10%, respectively. All procedures were performed under the manufacturers' instructions for the analyses. The absorbance at 405 nm was recorded by using a microplate reader.

The statistical analyses were carried out with the Statistical Package for the Social Sciences soft-ware package for Windows, Version 22.0 (SPSS, Chicago, IL, USA). The differences between the groups were determined with the Mann-Whitney U test. The correlations between the sarcoidosis patients and healthy controls were analyzed by the Spearman's rank correlation test. The demographic and clinic data of the study groups and the plasma levels of CLU and α-klotho were given as median and range. A p-value less than 0.05 was considered statistically significant.

RESULTS

Based on the exclusion criteria, a total of 80 participants were recruited into the study. The plasma CLU levels of sarcoidosis patients and the healthy controls were found as 309.73±40.68 ng/mL and 117.86±102.03 ng/mL, respectively. The plasma CLU levels were observed to be elevated in the healthy group (p=0.005). The plasma levels of α-klotho were measured as 5.34±7.30 ng/mL in the sarcoidosis patients group and 7.21±9.84 ng/mL in the healthy controls. While no significant p values were determined (p=0.338), a minimal decrease was

Table 1. Comparison of plasma clusterin and α-klotho levels and some parameters in sarcoidosis patients and healthy controls

Parameters	Sarcoidosis Group (n=40)	Healthy Controls (n=40)	p
Age (yrs), mean	52.10±12.60	37.40±18.20	0.058
Sex	male, 12 (30%)	male, 12 (30%)	1.00
	female, 28 (70%)	female, 28 (70%)	
Plasma clusterin, (ng/mL)	mean: 309.73±40.68	mean: 117.86±102.03	
	median: 303.280	median: 99.810	0.005*
	range: (101.15 - 509.50)	range: (99.15 - 275.00)	
Plasma α-klotho, (ng/mL)	mean: 5.34±7.30	mean: 7.21±9.84	
	median: 4.980	median: 3.305	0.338
	range: (1.77 - 9.16)	range: (1.15 - 16.51)	
Ca, (mg/dL)	9.25±0.57	8.48±0.34	0.436
ESR (mm/h)	22.58±16.7	18.21±46.3	0.237
Hb, (g/dL)	12.93±1.02	14.06±1.50	0.012*
MCV	82.39±6.97	85.7±4.55	0.090
CRP, (mg/dL)	10.20±12.44	9.32±26.14	0.129
PLT, Count (106)	293200±657.30	276666±689.37	0.733
MPV	9.60±1.44	10.14±1.57	0.170
Stage 1 Sarcoidosis	10 (25%)		
Stage 2 Sarcoidosis	26 (65%)		
Stage 3 Sarcoidosis	3 (7.5%)		
Stage 4 Sarcoidosis	1 (2.5%)		
Extrapulmonary Involvements			
None	29 (72.5%)		
Skin	4 (10%)		
Eye	1 (2.5%)		
Nervous system	1 (2.5%)		
Löfgren	1 (2.5%)		
Heart	4 (10%)		

Ca: Calcium, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, MCV: Mean corpuscular volume, MPV: Mean platelet volume, PLT: Platelet, *A p value of <0.05 was considered as significant

Table 2. Correlation of the laboratory parameters according to plasma clusterin and α- klotho levels in sarcoidosis patients

Parameters	Clusterin		α-klotho	
	r	p-value	r	p-value
Calcium (Ca)	-0,050	0.099	-0,265	0.761
ESR	0,036	0.169	0,222	0.824
Hemoglobin (Hb)	-0,187	0.477	-0,116	0.249
MCV	0,220	0.715	0,060	0.173
CRP	0,003	0.518	-0,105	0.985
PLT Count (106)	-0,052	0.440	-0,125	0.749
MPV	-0,090	0.151	-0,231	0.580

Ca: Calcium, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, MCV: Mean corpuscular volume, MPV: Mean platelet volume, PLT: Platelet

Table 3. Predictive power of clusterin and α-klotho in sarcoidosis patients

	cut-off value	AUC	sensitivity	specificity	PPV	NPV
clusterin	23	0.881 (0.811-0.951)	67.5%	72.5%	74.50%	66.89%
α klotho	1,05	0.387 (0.313-0.462)	100%	95%	100%	78.71%

AUC: Area under ROC curve, PPV: Positive predictive value, NPV: Negative predictive value. *Significant as p<0.001

observed in terms of the plasma α-klotho levels in the patients group, compared to the healthy controls (Table 1). Hemoglobin levels were also measured as 12.93±1.02 g/dL in the sarcoidosis group and 14.06±1.50 g/dL among the controls. The hemoglobin levels of sarcoidosis patients were seen to be lower, compared with the control group (p=0.012). The clinic characteristics and findings of both groups are shown in Table 2. In addition, the predictive power and ROC analysis of CLU and α-klotho are given as Table 3 and Figure 1 (respectively), and also histogram of CLU in Figure 2.

DISCUSSION

Sarcoidosis is a multifactorial disease with unknown aetiology and characterized by non-caseous granulomatous inflammation. The aim of the present study was to determine the plasma CLU and α-klotho levels, and to assess the potential diagnostic role of these biomarkers in the patients

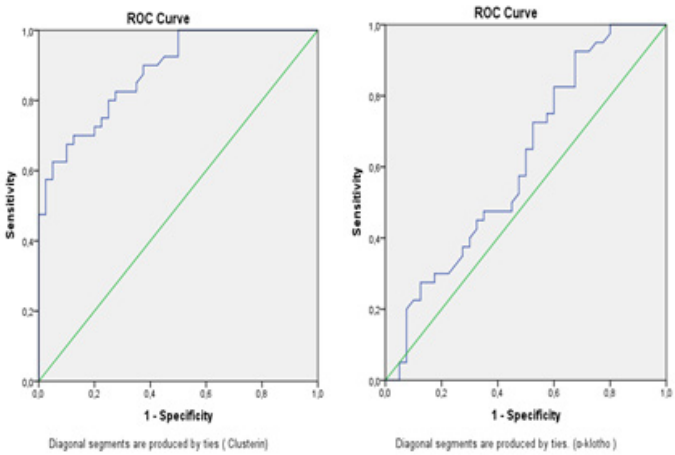

Figure 1. Receiver operating characteristic (ROC) analyses for clusterin and α-klotho

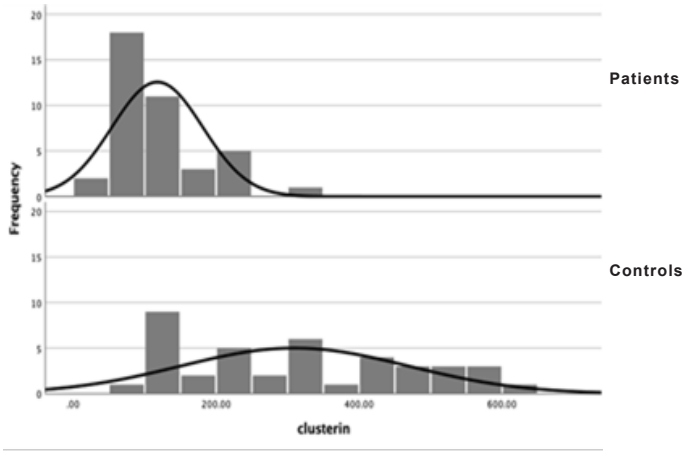

Figure 2. Histogram of clusterin in both groups

with sarcoidosis. Described by the formation of immune granulomas in the organs, sarcoidosis is a condition generally affecting the respiratory system (17). Determining the epidemiology of sarcoidosis is quite difficult due to the unknown causes, lack of precise definition and differences in the presentation for the diagnosis. As a multi-system granulomatous disorder, sarcoidosis is characterized by a T-helper response in which activated macrophages CD4 and lymphocytes accumulate in affected organs (18). In a study performed by Prior et al., it was reported that macrophages and T cells release a wide spectrum of mediators, including chemokines, cytokines and oxygen radicals involved in the pathogenesis of sarcoidosis (19). While the increased oxidative stress was characterised by the abnormality of elevated lipid situation, several oxidative stress markers and lipid situations were significantly linked with sarcoidosis (20).

Recent studies have evaluated the role of CLU in the pulmonary disorders and other related diseases. Several studies have also proposed that the secreted CLU protects cells against various conditions, such as oxidative stress and ionizing radiation. In another study, Carnevali et al. concluded that CLU has a protective role in cigarette smoke-induced oxidative stress in lung fibroblasts (21). Also, a study determined overexpressed CLU levels in non-small cell lung cancer (22). Several studies determined the increased arterial stiffness in sarcoidosis, reflecting an early stage of atherosclerosis. In sarcoidosis, chronic inflammation is one of the fundamental reasons for the atherosclerotic vascular conditions (23). In the study by Aciksari et al., it was concluded that the patients with sarcoidosis had significantly elevated endocan levels and lower brachial arterial flow-mediated dilation than those of the healthy group (24). The same study also proposed that the elevated levels of endocan may be a potential biomarker for the vascular dysfunction in sarcoidosis.

In a recent study, serum adiponectin levels have been emphasized to be higher in sarcoidosis patients, compared to the control group (25). According to the study, a potantial predictive role of adiponectin may be associated with some clinical features of sarcoidosis. As similar to the findings of this study, we also determined in our study that plasma CLU levels of sarcoidosis patients were higher than those of the healthy control group (309.73±40.68 and 117.86±102.03 ng/mL, respectively) (p=0.005).

The α-klotho in the circulation exhibits some physiological activities, such as anti-senescence, anti-inflammatory and anti-fibrotic features (26). In an animal study performed on mice, α-klotho deficiency was reported to lead to a shortened lifespan and lung emphysema consistent with aging (27). These results may indicate that α-klotho may have physiological effects on the pulmonary system. Recently, α-klotho has been shown to protect the lungs against the injuries by improving the endogenous antioxidative capacity of pulmonary epithelial cells. While α-klotho is mostly expressed in human airway epithelium, the reduced levels of this protein are observed in the patients with COPD.

The changes occuring in COPD are associated with increased inflammation, oxidative stress and apoptosis in airway epithelial cells (28). In the study by Buendia-Roldan et al., the decreased levels of serum α-klotho were reported to be associated with the reduced lung function in the patients with interstitial lung abnormalities (29). In our study, a decreased plasma α-klotho level was observed in the sarcoidosis group than that of the healthy group, and the difference was not statistically significant (5.34±7.30 and 7.21±9.84 ng/mL, respectively) (p=0.338).

Additionally, hemoglobin levels of sarcoidosis patients were also found to be lower, compared with the healthy control group (p=0.012). From the findings of the present study (Table 2), the clinical and laboratory parameters of both groups are seen not to be statistically different in comparison of the plasma CLU and α-klotho levels.

The present study was performed only in a single province, and the number of study population was limited. For this reason, more comprehensive studies with larger populations are needed to shed light on the entity.

CONCLUSION

The present study demonstrated that the patients with sarcoidosis have higher plasma concentrations of CLU than the healthy subjects. Moreover, the increased concentrations of CLU are positively associated with sarcoidosis and could be a predictive biomarker in the prognosis and diagnosis of sarcoidosis. Further comprehensive and experimental studies will also help determine whether CLU and α-klotho would be of potential therapeutic benefits in the treatment of sarcoidosis.

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Address correspondence to: *Turan Akdag, Necmettin Erbakan University, Meram Vocational School, Konya, Turkey*
E-mail: *turanakdag570@gmail.com*
Phone number: *+905056597350*

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