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ORIGINAL ARTICLE

Could Hemokinin-1 (HK-1) be a Novel Candidate Biomarker for Sarcoidosis?

Hemokinin-1 (HK-1) Sarkoidoz için Yeni Bir Aday Biyobelirteç Olabilir mi?

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ABSTRACT

Aim: Sarcoidosis is a systemic inflammatory disease and characterized by the presence of non-caseating granulomas which may affect all organs in the body. Some studies suggest an association between peptides and sarcoidosis. The goal of the study was to investigate the biomarker values of serum hemokinin-1 (HK-1) and adropin levels in sarcoidosis and to assess their role in the disease course.
Patients and Methods: The study was carried out in in the Chest Diseases Clinic, Faculty of Medicine hospital, Necmettin Erbakan University, Konya between April 2021 and February 2022. Thirty-eight patients with diagnosed sarcoidosis (14 men and 24 women) and 38 healthy (14 men and 24 women) individuals were enrolled in the study. Demographic characteristics, age, gender, disease duration, and extrapulmonary involvement of the patients were enrolled. HK-1 and adropin levels were measured via the sandwich ELISA (enzyme linked immunosorbent assay) method.
Results: HK-1 level was elevated in the sarcoidosis patients than in the healthy individuals, these differences were significant statistically (0.67±0.23 and 0.54±0.24 ng/ml, p=0.012). The serum levels of adropin were measured as 207.84±246.72 ng/L in the sarcoidosis patients group and 151.16±171.76 ng/L in the healthy individuals group. No significant differences were determined in terms of the adropin levels in the patient's group when compared to the healthy individuals group (p=0.076). Serum adropin were negatively correlated with BAL CD4+ levels (r=-,880 and p=0.002) and positively correlated with BAL CD8+ levels (r=,697 and p=0.037).
Conclusions: At the study, it is determined that patients with sarcoidosis show significantly higher HK-1 levels than healthy controls, and HK-1 may be a useful non-invasive diagnostic biomarker for this disease. From the literature, serum HK-1 and adropin levels have not been investigated in sarcoidosis, yet. To clarify this topic, further and larger size studies are needed.

Keywords: Sarkoidoz, hemokinin-1, adropin

ÖZ

Amaç: Sarkoidoz, vücuttaki bütün organları etkileyebilen, kazeifiye olmayan granülomların varlığı ile karakterize, nedeni bilinmeyen sistemik inflamatuar bir hastalıktır. Bazı çalışmalar peptitler ve sarkoidoz arasında bir ilişki olduğunu önermektedir. Bu çalışmanın amacı sarkoidozda serum hemokinin-1 (HK-1) ve adropin düzeylerinin tanısal değerlerini araştırmak ve hastalıkta rolünü değerlendirmektir.
Hastalar ve Metod: Çalışma Nisan 2021-Şubat 2022 tarihleri arasında Göğüs Hastalıkları Kliniği, Tıp Fakültesi Hastanesi, Necmettin Erbakan Üniversitesi, Konya'da gerçekleştirildi. Çalışmaya sarkoidoz tanılı 38 hasta (14 erkek, 24 kadın) ve 38 sağlıklı (14 erkek, 24 kadın) birey alındı. Hastaların demografik özellikleri, yaşı, cinsiyeti, hastalık süresi ve akciğer dışı tutulumu kaydedildi. HK-1 ve adropin düzeyleri, sandviç ELISA (enzime bağlı immünosorbent) yöntemi ile belirlendi.
Bulgular: Sarkoidozlu hastalarda HK-1 seviyesi sağlıklı bireylere göre daha yüksekti, aradaki fark istatistiksel olarak anlamlıydı (0,67±0,23 ve 0,54±0,24 ng/ml, p=0,012). Serum adropin düzeyleri sarkoidoz hasta grubunda 207,84±246,72 ng/L, sağlıklı kontrol grubunda 151,16±171,76 ng/L olarak belirlendi. Sarkoidozlu hastalarının adropin seviyeleri ise sağlıklı bireylere göre anlamlı fark belirlenmedi (p=0,076). Serum adropin seviyeleri, BAL CD4+ seviyeleri ile negatif (r=-,880 ve p=0.002) ve BAL CD8+ seviyeleri ile pozitif korrelasyon gösterdi (r=,697 ve p=0.037).
Sonuç: Çalışmada sarkoidozlu hastaların sağlıklı kontrollere göre anlamlı olarak daha yüksek HK-1 seviyeleri gösterdiği ve HK-1'in bu hastalık için invaziv olmayan yararlı bir tanısal biyobelirteç olabileceği belirlendi. Literatürde henüz sarkoidozda serum HK-1 ve adropin düzeyleri araştırılmamıştır. Bu konuyu açıklığa kavuşturmak için daha fazla ve geniş çaplı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Sarkoidosis, hemokinin-1, adropin

Introduction

As a multisystem inflammatory disease, sarcoidosis can affect one or more organs (lung, skin, nervous system, eyes, heart, liver, etc.) and is characterized by epithelioid non-caseating granulomas of unknown etiology (1). As clinic, sarcoidosis affects mostly the pulmonary system (90%). Symptoms include cough, dyspnea, and chest pain (2). The clinical presentation of sarcoidosis is related to epidemiological factors; age, gender, and race. At the same time, the duration of the disease and the anatomical region involvements are important in terms of clinical presentation (3). While it is reported that Scandinavians have a high incidence of 19/100.000, the incidence is estimated to be as 5-10/100.000 in Turkey (4). While it is reported to have a high incidence of 19/100,000 in Scandinavians, the incidence is estimated to be 5-10/100,000 in Turkiye. The identification of sarcoidosis is settled by the presence of compatible clinical and radiological findings, histopathologically noncaseating granulomatous inflammation, and exclusion of other causes of granulomatous inflammation. For the definitive of disease, clinical and radiological findings

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and the presence of histopathologically noncaseating granulomas are not sufficient as pathognomonic (5). Nowadays, many biomarkers are being investigated to predict progressive disease in sarcoidosis. A study demonstrated that increased tumor necrosis factor-a production by bronchoalveolar cells is associated with persistent disease. It is also reported that other proinflammatory cytokines such as osteopontin, IL-1 (interleukin-1), IL-6, and macrophage migration inhibitory factor levels are increased in sarcoidosis disease (6,8). In a previous study, Ahmadzai et al. declared that elevated neopterin levels were observed in patients with sarcoidosis when compared to control subjects (9).

Tachykinins are a family of neuropeptides that have important effects on pain, immunity, and inflammatory situations (10). Encoded by the preprotachykinin B/Tac4 gene, hemokinin-1 (HK-1) is a part of the tachykinin's and consists of 11 amino acids (11). With its broad presence in the human body, HK-1 displays different pathophysiological and physiological functions such as immune regulation, respiratory functions, and tumorigenesis (12). It also plays a role in many physiological events such as inflammation, hematopoietic cell development, and vasodilation (13). A study stated that HK-1 is formed by macrophages and bronchial cells, and also causes the bronchi to contract (14).

Adropin (coded by the energy homeostasis related gene) is synthesized as a precursor polypeptide containing that contains 76 aminoacids (molecular weight of ~4.5 kDa). As a highly protected polypeptide, it displays important roles in physiological phenomena such as endothelial function, insulin sensitivity, and metabolic balance (15). From the studies, adropin was detected in peripheral tissues such as the lung, heart, muscles, kidney medulla, and breast cancer cells (16).

Our study goal is to measure circulating HK-1 and adropin levels in sarcoidosis and to discuss their relation with the mentioned disease. According to the knowledges, the research is the first preliminary study aiming to investigate whether these biomarkers can be used in the diagnosis and exclusion of sarcoidosis.

Patiens and Methods

Aged between 18-65 years, thirty-eight sarcoidosis patients (14 men and 24 women) and 38 healthy subjects (14 men and 24 women) were enrolled. The study was conducted in the Chest Diseases Clinic, Faculty of Medicine hospital, Necmettin Erbakan University, Konya between April 2021 and February 2022. The healthy subjects were recruited from individuals who applied to a university hospital for routine control. Demographic characteristics, gender, extrapulmonary involvement of the patients, and clinical assessments were registered before the analysis. Individuals with acute infection, metabolic disorder, heart disease, kidney disease, diabetes mellitus, hypertension, and any other known diseases were excluded from the study. Blood samples received from participants were centrifuged (4000 rpm) for 15 minutes at +4°C. The sera were put in Eppendorf tubes and stored at -80°C until the assay. Approval for the study was obtained from the Non-Invasive Clinical Research Ethics Committee of the Faculty of Medicine in Necmettin Erbakan University (Date: 19/02/2021, decision no:2021/3104). All participants gave their informed and signed consent for inclusion.

Measurements of serum HK-1 and adropin

According to the manufacturer's instructions protocols, serum HK-1 and adropin levels were measured via the sandwich ELISA (enzyme linked immunosorbent assay) method. Serum HK-1 was determined via a human ELISA kit (Tachykinin 4/hemokinin-1, MyBioSource, San Diego, ABD Cat No: MBS2602776). The declared sensitivity of the assay was 0.05 ng/ml with a linearity range of 0.156 ng/ml-10 ng/ml. Serum adropin was also determined via a human ELISA Kit (Human Adropin, Bioassay Technology Laboratory, Shanghai, China Cat No: E3231Hu). The sensitivity of the assay was 2.49 ng/L with a linearity range of 5 ng/L-1000 ng/L. The absorbances of the specimens were determined via a microtiter plate reader (450 nanometer)(ELx800TM, Bio-Tech Instruments, USA).

Statistical analysis

The statistical analyses were performed with IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA). The data was presented using means, mean±standard deviation, and median values. Homogeneity of the variances and normality was controlled with the Levene test and Shapiro-Wilk test, respectively. In the analysis of the measurement values between the groups, the Student-t test was used when the parametric test conditions were met in the groups with two independent variables, and the Mann-Whitney U test was used if not. The relation between two continuous variables was determined via the Pearson correlation coefficient, and if not met, the Spearman correlation coefficient was used. Receiver operating characteristic analysis, the area under the curve, cut-off scores, sensitivity, and selectivity values were determined. The significance level was considered as $p<0.05$.

Table 1: Characteristics of participants

Parameters	Sarcoidosis patients (n=38)	Healthy subjects (n=38)	p
Age, (*mean±standart deviation)*	48.27±18.25	45.52±12.34	-
Gender (n=76)	Men, 14 (36.84%) Women, 24 (63.16%)	Men, 14 (36.84%) Women, 24 (63.16%)	-
St. 1 Sarcoidosis St. 2 Sarcoidosis St. 3 Sarcoidosis St. 4 Sarcoidosis	10 (26.32%) 21 (55.26%) 4 (10.53%) 3 (7.89%)		
Extrapulmonary involvements None Skin Eye Nervous system Löfgren Heart	26 (68.42%) 4 (10.53%) 3 (7.89%) 2 (5.26%) 2 (5.26%) 1 (2.64%)		
ESR *(mm/h)*	33.54±22.37		
Blood CD4+	36.21±9.23		
Blood CD8+	26.12±7.12		
BAL CD4+	70.4±11.46		
BAL CD8+	17.76±4.61		
Spontaneous Remission	yes 11 39.3 no 17 60.7 total 28 100		

ESR: Erythrocyte sedimentation rate, BAL: Bronchoalveolar lavage, CD4+: Cluster of differentiation 4, St: stage

Table 2: Comparison of HK-1 and adropin values in sarcoidosis and healthy groups

	Sarcoidosis patients		Healthy subjects			
	Mean±Std. Deviation	Medyan (Min-Max)	Mean±Std. Deviation	Medyan (Min-Max)	TS	p
HK-1 (ng/ml)	0.67±0.23	0.64 (0.26-1.39)	0.54±0.24	0.51 (0.24-1.22)	-2.514	0.012€*
Adropin (ng/L)	207.84± 246.72	90.50 (55.01-842.5)	151.16± 171.76	73.27 (2.72-535.82)	-1.774	0.076€

*p<0.05€, HK-1: hemokinin-1, TS: Test statistics

Table 3: Correlations between HK-1 and adropin

n=76		Adropin	HK-1	Age	AO	ESR	Blood CD4+	Blood CD8+	BAL CD4+
HK-1	r	-0,039							
	p	0,767							
Age	r	-0,018	,255						
	p	0,892	0,059						
AO	r	-0,137	0,134	,886					
	p	0,496	0,504	0,061					
ESR	r	-0,279	0,159	0,284	0,234				
	p	0,136	0,401	0,120	0,254				
Blood CD4	r	0,043	0,030	0,296	0,221	-0,003			
	p	0,913	0,940	0,422	0,546	0,972			
Blood CD8	r	0,367	-0,618	0,309	0,279	0,171	-0,256		
	p	0,331	0,076	0,458	0,436	0,646	0,514		
BAL CD4+	r	-,880*	0,290	-0,657	-0,634	0,148	-0,137	-0,457	
	p	0,002	0,450	0,072	0,085	0,728	0,791	0,192	
BAL CD8+	r	,697*	-0,149	-0,076	-0,067	0,143	-0,375	0,286	-0,588
	p	0,037	0,701	0,853	0,888	0,654	0,367	0,437	0,123

p<0.05, AO: age of onset

Table 4: AUC, cut-off, sensitivity, and selectivity values

	Cut-off	AUC (95% CI)	p	Sensitivity	Specificity	PPV	NPV
HK-1	0.422	0.689 (0.556-0.802)	0.007*	43.3	93.3	6.7	62.2
Adropin	53.442	0.33 (0.499-0.754)	0.080	40.0	100.0	100	62.5

AUC: area under the curve, CI: confidence interval, NPV: negative predictive value, PPV: positive predictive value

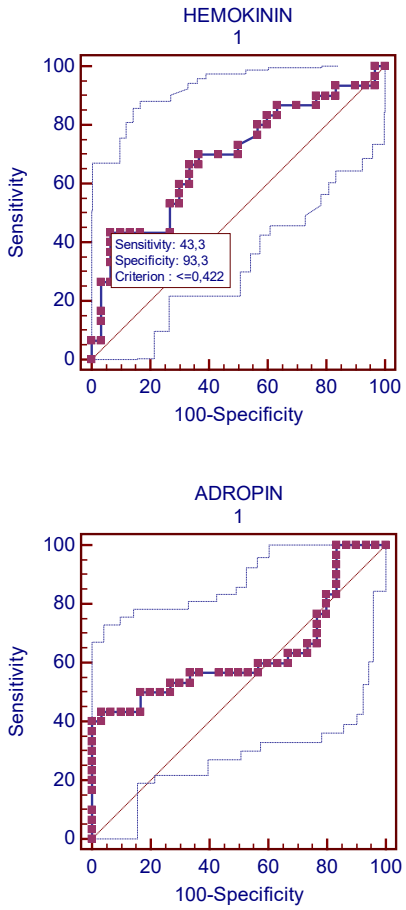

Figure 1: ROC analyses of HK-1 and adropin

Results

The mean ages of sarcoidosis patients and healthy subjects were found as 48.27 and 45.52 years, respectively. All the characteristics are shown in Table 1. Serum levels of HK-1 were measured as 0.67±0.23 ng/ml in the sarcoidosis patient group and 0.54±0.24 ng/ml in the healthy subjects. HK-1 levels were elevated in sarcoidosis patients when compared to healthy subjects (p=0.012, Table 2). The serum adropin level was higher in the sarcoidosis patients than the healthy subjects, but it was not significant (207.84±246.72 and 151.16±171.76 ng/L, p=0.076 respectively).

Serum adropin levels were negatively correlated with BAL CD4+ levels (r=-,880 and p=0.002) and positively correlated with BAL CD8+ levels (r=,697 and p=0.037, Table 3). Also, AUC, selectivity, ROC, and sensitivity values are shown in Table 4 and Figure 1.

Discussion

Sarcoidosis is characterized by non-caseating granulomatous inflammation in the involved regions and its etiology has not been fully elucidated (17). The incidence of sarcoidosis is widespread and its prevalence is around 40 per 100,000 in the world. The disease typically affects those under the age

of 40. Also, it is declared that sarcoidosis disease is more prevalent in women (18). Since the commonly affected organs are the lungs, skin, and eyes, some hypotheses have been proposed that airborne infectious or non-infectious antigens may cause sarcoidosis (19). At the onset of sarcoidosis disease, mononuclear cells consisting of CD4+ T cells and monocytes/macrophages are collected first in the involved organs. The most critical event is the binding of CD4+ T cells and antigen presenting cells (APC) to initiate granuloma formation (20).

Numerous biomarkers have been proposed for sarcoidosis disease, but none of them seem to be universally recognized in clinical practice. Chitotriosidase enzyme which generates by activated macrophages displays roles against nematodes, insects, and fungi. In a recent study, Bennett et al. reported that chitotriosidase levels were elevated in patients with sarcoidosis (p<0.0001) correlating with disease activity, severity, and multiorgan dissemination (21). Moreover, a previous study supposed that the brain natriuretic peptide (BNP) level may be a useful tool for identifying cardiac involvement in sarcoidosis patients (22). Nowadays, researches on this subject with different and newly defined markers are ongoing.

The tachykinins modulate the immune response and regulate the production of some cytokines which include TNF-a, IL-1, and IL-6 to proliferation and inflammatory responses. Studies have reported that tachykinins are widely involved in the onset and progression of lung diseases such as bronchitis (23) and asthma (24). A recent study revealed that HK-1 can cause degranulation of the leukocyte adhesion deficiency-2. These findings demonstrated that HK-1 plays a role in the pathogenesis of chronic obstructive pulmonary disease and asthma (14).

As member of the tachykinin family, HK-1 has been identified in non-neuronal cells such as immune and pulmonary cells (25,26). A previous study proposed that HK-1 which is generated by lung macrophages and bronchial cells might cause the contraction of isolated human bronchi (14). Recently, hemokinin-1 has been described and characterized by different aspects of inflammation and investigated in animal models of allergic airway inflammation, but the role of HK-1 in lung diseases is unknown (27). In the study, serum HK-1 level was elevated in the sarcoidosis patients when compared to the healthy subjects, and this difference was significant (p=0.012).

Adropin is a hormone (consisting of 76 amino acids) with a molecular weight of 7,927 kDa and has an important effect on controlling energy homeostasis (28). As a polypeptide, it shows a remarkable role in different metabolic topics and inflammation. (29). Adropin is expressed in multiple tissues, including the lung, liver, aorta, small intestine, heart, kidney, skeletal muscle, brain, and spleen (30). The altered concentration of adropin accompanies many diseases such as gestational diabetes mellitus (31), non-alcoholic fatty liver disease (32), and endothelial dysfunction (33). In a study, Ganesh-Kumar et al. measured adropin deficiency in myeloperoxidase specific antineutrophil cytoplasmic antibody-related lung injury (34).

Our study determined that serum adropin level was high in the sarcoidosis patients when compared to the healthy subjects, but the differences was not significant (p=0.076). The relation between adropin and BAL CD4+, and BAL CD8+ levels had not been investigated previously. In our study, adropin levels were negatively correlated with BAL CD4+ levels (r=-,880 and p=0.002) and positively correlated with BAL CD8+ levels (r=,697 and p=0.037). No statistically significant correlation was found between other laboratory findings according to the levels of studied biomarkers (Table 3).

Conclusion

According to the study, patients with sarcoidosis show significantly higher hemokinin-1 levels than the healthy controls. In the ROC analysis, the specificity was high and the sensitivity lower. Therefore, comprehensive studies are needed to be able to use as a useful non-invasive diagnostic biomarker for this disease. In the literature, it seems that these biomarkers have not been investigated in sarcoidosis, yet. To clarify this topic, further and larger size investigations are required.

Conflict of interests: No competing interests.

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Ethical approval: The Non-Invasive Clinical Research Ethics Committee of the Faculty of Medicine in Necmettin Erbakan University (Date: 19/02/2021, decision no:2021/3104)

Authorship: Concept – CK, TA Design - CK, TA Supervision – CK, TA Funding - None Materials – CK Data collection &amp/or processing – CK, TA Analysis and/or interpretation – CK, TA Literature search – CK, TA Writing – CK, TA Critical review – CK, TA

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