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Original Article

Monocyte/HDL ratio in sarcoidosis patients without treatment

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Abstract

Aim: This study examined the effects of monocyte/high-density lipoprotein cholesterol (HDL-C) ratio (MHR) and other inflammatory markers in patients with sarcoidosis not receiving treatment. To our knowledge, this is the first study on the relationship between sarcoidosis and MHR.

Material and Methods: This study included 53 patients with sarcoidosis who were followed at a single, outpatient tertiary-care centre. Data on patient demographics (age and gender), disease characteristics (duration of disease, radiographic stage, treatments); pulmonary function tests (% predicted values for forced vital capacity [FVC], forced expiratory volume at 1 second [FEV_1], diffusing capacity of the lungs for carbon monoxide [DLCO], alveolar volume [VA], forced expiratory flow [25–75% and at 50%; FEF] [FEF_{25-75}]), blood biochemistry and hemogram findings were retrieved from hospital records.

Results: Mean ± SD patient age was 51.13 ±1 1.94 years. Of the 53 patients, 42 were female and 11 were male. When compared with MHR ratio and pulmonary function test parameters, there was a negative correlation with FEV_1% (P = 0.043, r = −0.279) and DLCO% (P = 0.009, r = −0.360). There was no significant correlation between FVC, FEV_{25-75} or VA. No significant correlation was found between blood calcium, urinary calcium, SACE (serum angiotensin converting enzyme) values and MHO ratio.

Conclusions: Large-scale prospective studies are needed to determine if the use of MHR as an indicator of inflammation and activation would be helpful in the diagnosis and monitoring of patients with sarcoidosis.

Keywords: Inflammation; Monocyte/HDL ratio; sarcoidosis

INTRODUCTION

Sarcoidosis is a systemic granulomatous disease that affects people of all ages around the world, with the highest incidence in those between the ages of 20 and 40 (1). There are significant racial and gender differences in disease prevalence, incidence, and severity. The highest annual incidence has been observed in northern European countries, at 5 to 40 cases per 100,000 people per year (2,3). The incidence of sarcoidosis in our country has been reported as 4/100.000 (4).

Sarcoidosis as a systemic granulomatous disease of unknown cause that primarily affects the lungs. However, the abnormal inflammatory disease process may affect any organ and tissue of the body, most often the lymph nodes of the thorax and neck, skin and liver (5,6).

The diagnosis of sarcoidosis requires an appropriate clinical picture, histological findings of non-caseating granulomas and exclusion of other diseases capable of producing a correlative histological or clinical picture (7,8). A proposed new marker for the detection of systemic inflammation is the monocyte/high-density lipoprotein cholesterol (HDL-C) ratio (MHR) (9,10).

Circulating monocytes as a source of various cytokines and molecules; It interacts with platelets and endothelial cells, causing the accumulation of inflammatory, pro-thrombotic pathways. HDL-C eliminates the pro-inflammatory and pro-oxidant effects of monocytes by inhibiting the migration of macrophages. Therefore, MHR may indicate the inflammatory status of a patient (10-12).

These inflammatory markers can be detected in the complete blood counts (CBC) and biochemical parameters routinely screened in patients with sarcoidosis. There are conflicting studies on the relationship between sarcoidosis and inflammatory markers. CBC is useful test and MHR parameter could be a practical for evaluate sarcoidosis patients inflammatory status. Cholesterol parameters and CBC test being cheap and easily available in all health centers make MHR parameter advantageous

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in the diagnosis of sarcoidosis. This study examined the effects of MHR and other inflammatory markers in patients with sarcoidosis not receiving treatment. To our knowledge, this is the first study on the relationship between sarcoidosis and MHR.

MATERIAL and METHODS

Study population

This study included 53 patients with sarcoidosis who were followed at a single, outpatient tertiary-care centre.

Patients diagnosed with sarcoidosis who applied to our chest diseases clinic in 2019 were included in this study. The number of patients meeting the exclusion criteria was 53 and our study was planned retrospectively. Patient consent was obtained during the outpatient applications of the patients. Permission and approval for the use of patient data for publication purposes was obtained from the institutional ethics committee (Date of Approval: 04.11.2019; Reference number/Protocol No:2019/239).

Assessments

Data on patient demographics (age and gender), disease characteristics (duration of disease, radiographic stage, treatments); pulmonary function tests (% predicted values for forced vital capacity [FVC], forced expiratory volume at 1 second [FEV_1], diffusing capacity of the lungs for carbon monoxide [DLCO], alveolar volume [VA], forced expiratory flow [25–75% and at 50%; FEF] [FEF_{25-75}]), blood biochemistry and hemogram findings were retrieved from hospital records.

All CBC analyses were conducted using a Beckman Coulter LH 780 analyser in the haematology laboratory of the tertiary-care centre. Blood in standardised tubes (2 ml) including 0.04 mL of 7.5% K3 salt of ethylenediaminetetra-acetic acid (EDTA) was used for analysis. Baseline MHR was calculated by dividing the monocyte count by the HDL-C level.

Exclusion criteria

Patients <18 years of age, under treatment for sarcoidosis and receiving hyperlipidemia treatment were excluded from the study. Moreove, patients with Crohn's diseases, rheumatoid arthritis, vasculitis, thyroid hormone abnormalities, hepatic, renal, hemolytic disorders, malignancy or coronary artery disease were excluded from the study.

Statistical analysis

The SPSS-21 programme was used for statistical analyses. Descriptive statistics (mean ± standard deviation, median, minimum, maximum) of all variables were calculated. First, the normality of distribution of variables was examined by the Kolmogorov–Smirnov test. The chi-square test was used to examine the relationships between categorical variables, and the Spearman correlation test was used in all correlation analyses. A P-value <0.05 was considered statistically significant.

RESULTS

Mean ± SD patient age was 51.13 ±1 1.94 years. Of the 53 patients, 42 were female and 11 were male. Overall, stage 1, 2, and 3 sarcoidosis was evident in 8 (15.1%), 41 (77.4%), and 4 (7.5%) patients, respectively.

The mean FEV1 value was 94.1%, the FVC value was 101.4%, the DLCO value was 81.0%. General features of sarcoidosis patients are shown in Table 1. The mean diagnosis period of the patients was 4.56 years (minimum 6 months-maximum 20 years).

Table 1. General features of sarcoidosis patients

Number of patients (n=53)	N (%) or Mean±SD (min-max)
Gender	
Male	11 (20.8)
Female	42 (79.2)
Age (year)	51.1±11.9 (26-76)
Medical properties	
Diagnosis time, (year)	4.56±4.36 (0-20)
Radiographic stage	
Stage 1	8 (15.1)
Stage 2	41 (77.4)
Stage 3	4 (7.5)
Pulmoner Function Tests	
FVC, (ml),(% predicted)	101.4±14.2 (70-130)
FEV_1, (ml),(% predicted)	94.1±16.3 (56-126)
FEF-25/75 (L/s) (%predicted)	67.7±23.09 (25-124)
DLCO, (ml/mmHg/dk) (%predicted)	81.0±14.5(56-110)
VA, (ml) (%predicted)	88.2±11.4 (66-123)
Laboratory parameters	
Serum creatinine (mg/dL)	0.61± 0.13 (0.40-1.04)
SACE (U/l)	48.5±23.7 (7.5-100.6)
24 hour Urine Calcium (mmol/d)	9.12±6.69 (1.60-29.80)
Blood Calcium (mg/dl)	9.73±0.52 (8.70-11.00)
LDL cholesterol (mg/dL)	129±35.8 (58-200)
HDL cholesterol (mg/dL)	46.3±8.8 (29.0-64.0)
Triglyceride (mg/dL)	166.9±76.2 (55.0-489.0)
Cholesterol (mg/dL)	210.1±45.9 (128.0-327.0)
Monocyte (x109/L)	579.4±157.4 (270.0-1090.0)
MHR	13.01±4.30 (4.57-23.33)

Data were expressed as N (%) or Mean±SD (minimum-maximum); FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume at 1 s; V: alveolar volume FEF25-75; forced expiratory flow (25-75% and at 50%; FEF); SACE: Serum Angiotensin Converting Enzyme; MHR: Monocyte/Hdl Ratio; DLCO (ml/mmHg/dk), diffusing capacity of the lungs for carbon monoxide

When compared with MHR ratio and pulmonary function test parameters, there was a negative correlation with FEV_1% (P = 0.043, r = −0.279) and DLCO% (P = 0.009, r = −0.360) (Figure1). There was no significant correlation between FVC, FEV_{25-75} or VA. No significant correlation was found between blood calcium, urinary calcium, SACE (serum angiotensin converting enzyme) values and MHO ratio (Table 2).

Table 2. Comparison of pulmonary function test and laboratory parameters with MHR

MHR	p,r	
FVC, (ml),(% predicted)	p	0.094
	r	-.233
FEV1, (ml),(% predicted)	p	**0.043**
	r	-0.279
FEF-25/75 (L/s) (%beklenen)	p	0.772
	r	-0.042
DLCO, (ml/mmHg/dk) (%predicted)	p	**0.009**
	r	-0.360
VA, (ml) (%predicted)	p	0.061
	r	-.264
Blood Calcium (mg/dl)	p	0.510
	r	0.092
24 hour Urine Calcium (mmol/d)	p	0.700
	r	0.056
SACE (U/l)	p	0.421
	r	0.120

DLCO (ml/mmHg/dk), diffusing capacity of the lungs for carbon monoxide; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in 1 Second; VA: Alveolar Volüme; FEF25-75: Forced Expiratory Flow (25-75% and at 50%; FEF)

DISCUSSION

In this study, we found a significant negative correlation between MHR, which is considered to be an inflammation marker, and FEV_1 and DLCO and we found no significant correlation was found between blood calcium, urinary calcium, SACE values and MHO ratio

Sarcoidosis is characterised by non-caseating granulomas consisting of activated T lymphocytes, epithelioid cells and multinucleated giant cells (MGC). These cells release chemokines and cytokines that lead to cellular proliferation and granuloma formation. The cytokine profile of active sarcoidosis is characterised by T helper 1 (Th1) prevalence (13-15).

The expression of IL-18 is increased at sites of chronic inflammation in infectious diseases, neoplasms and autoimmune disorders. Kieszko et al studied IL-18, an inflammation marker in bronchoalveolar lavage fluid (BALF), and found it to be significantly higher in sarcoidosis patients. In that study, no significant correlation was found between IL-18 levels and pulmonary function values (14). However, in the present study, we found a significant correlation between MHR and the pulmonary function parameters FEV_1 and DLCO. As the MHR value increased, it was seen that the FVC value was decreasing, although not statistically significant. The reason for the lack of statistical significance may be due to the low number of patients.

Oncostatin M (OSM) is a secreted cytokine involved in homeostasis and in diseases involving chronic inflammation (16). Guber A et al (17) measured OSM, which is thought of as part of the T cell–mediated inflammatory process, in BALF of 20 sarcoidosis patients and found that FEV_1 % was correlated with the percentage of activated mast cells, as well as with the percentage of OSM-positive mast cells. FVC and FEV_1/FVC correlated with activated mast cells. Direct correlation was found between clinical parameters including lung function tests (FEV_1 and FVC) and OSM secretion from mast cells in patients with sarcoidosis. These findings suggest that mast cells and OSM have a role in sarcoidosis. In our study, we found no significant correlation with SACE value, but did find a significant correlation with pulmonary function tests (PFTs) (DLCO, FVC).

Nitric oxide (NO) plays a key role in airways as a neurotransmitter, vasodilator and inflammatory mediator. Sarcoidosis is a multisystem disorder of unknown cause. The early sarcoid reaction is characterised by the accumulation of increased numbers of activated T cells and macrophages at sites of ongoing inflammation, notably in the lung. Sarcoid T lymphocytes bear the helper CD4 phenotype and spontaneously release interleukin-2 and interferon gamma (IFN-γ), which is able to induce the nitric oxide synthases pathway. Sarcoid alveolar macrophages release a great variety of cytokines, including tumour necrosis factor-α (TNF-α), which may upregulate activation of iNOS (13,18).

Ziora et al. (19) measured exhaled NO and found it to be high in sarcoidosis patients but not associated with the activity of the disease. They found no significant relationship between exhaled NO levels and FVC, but found poor correlation with DLCO. In our study, we did not find any correlation between MHR and FVC, but we found a significant negative correlation with DLCO.

The main immunocompetent cells in sarcoidal lesions are epithelioid cells and MGCs, both of which are derived from monocyte-macrophage lineage cells. Chemoattractant factors released from monocyte-macrophage lineage cells are important for the accumulation of T lymphocytes in sarcoidal lesions. Epithelioid cells and MGC are the main component cells of the mature lesions and are considered to be derived from monocyte-macrophage lineage cells. Thus, monocyte-macrophage lineage cells are key cells in the initiation, development, and maintenance of sarcoidal granulomatous lesions (20-22).

In a study by Mizuno et al; they further understand the relevance of monocytes in sarcoidosis. They examined

in vitro MGC formation (concanavalin A-stimulated mononuclear cells hücrelerin) using monocytes from sarcoidosis patients and healthy control subjects. They found that monocytes of sarcoidosis patients had a more heightened ability to form MGC than those of the control subjects. The higher fusion index in sarcoidosis patients was mainly due to the enhanced formation of the Langhans type, which are the predominant form of MGC in sarcoidal lesions. MGC formation from macrophages, induced by macrophage colony-stimulating factor (M-CSF) treated-monocytes, was also significantly greater in sarcoidosis patients than in other groups. They concluded that these findings suggest that peripheral blood monocytes in sarcoidosis patients may have the potential to form MGC easily in response to inflammatory stimuli (22).

Our study has some significant limitations. First, the sample size was small and did not include any patients with stage 4 sarcoidosis; moreover, we did not use a healthy control group. In addition, the patient groups were not homogeneous, therefore, there was no comparison between the groups.

CONCLUSION

While many cytokines, their receptors and gene polymorphisms have been investigated as potential prognostic factors in sarcoidosis, only a few may become useful in clinical practice. Large-scale prospective studies are needed to determine if the use of MHR as an indicator of inflammation and activation would be helpful in the diagnosis and monitoring of patients with sarcoidosis. In addition, we suggest that these studies should be performed in comparison with healthy groups and that patients in all stages of sarcoidosis should be included.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: Permission and approval for the use of patient data for publication purposes was obtained from the institutional ethics committee (Date of Approval: 04.11.2019; Reference number/Protocol No:2019/239).

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