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The Evaluation of The Relationship between The Radiological Pulmonary Stage of Sarcoidosis and Carotid Artery Intima Media Thickness Measurement on The Sarcoidosis Patients with Lung Involvement

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Abstract

Objective: Sarcoidosis is a disease which courses with noncaseating granulomas, and within the pathophysiology of which abnormal immune response, inflammation and oxidative stress are held responsible. Lungs are the organs which it mostly involves and the lung involvement is radiologically divided into stages. The present research aims to evaluate the relationship between the lung involvement stage of sarcoidosis and carotid intima media thickness measurement which is one of the indicators of subclinical atherosclerosis.

Materials and Methods: 48 sarcoidosis patients with isolated pulmonary involvement were included in the study. The patients are divided into four stages according to their radiological appearances. The carotid intima media thickness, laboratory and antropometric measurements of the patients are compared between their stages.

Results: Carotid intima media thickness is measured to be averagely 0,66 ± 0,19 mm. Carotid intima media thickness is observed to increase progressively from Stage-1 to Stage-4. The stages are found out to have significant differences among each other (p:0,000).

Conclusion: The radiological pulmonary staging of sarcoidosis and carotid intima media thickness measurement - albeit indirectly subclinical atherosclerosis - are found out to have a significant relationship.

Keywords: Sarcoidosis, Carotid intima media thickness measurement, Atherosclerosis

Introduction

Sarcoidosis is an autoimmune disease which can involve in plenty of organs and systems, particularly in lungs, and which histopathologically courses with noncaseating granulomas. While its etiology is still unknown, the pathologically responsible factors are as such: genetic origin, environmental factors, abnormal immune response, inflammation and oxidative stress [1, 2]. The most involved organs in sarcoidosis are lungs. Nearly 95% of the sarcoidosis patients have lung involvements [3]. Lung sarcoidosis is staged directly based upon the chest radiography findings. The most frequently used system in staging is Siltzbach staging system [4].

Atherosclerosis is both a progressive vascular disease and a risk factor for many cardiac diseases. The first phenomenon in atherosclerosis is an endothelial dysfunction. Endothelial dysfunction may arise due to many reasons such as trauma, inflammation, oxidative stress, immunological ones,

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etc. Endothelial dysfunction is followed by inflammation and proliferation processes, then, atheroma plaques are formed [5]. One of the methods used to diagnose atherosclerosis in the early stage is to measure carotid artery intima media thickness (CIMT). It is also shown that increased carotid intima media thickness is related to major cardiovascular diseases as well as atherosclerosis [6]. Previous studies suggest that the sarcoidosis patients have greater carotid intima media thickness than healthy people and increased risk of atherosclerosis [7]. The present study aims to investigate the relation between the pulmonary stage of sarcoidosis and atherosclerosis, albeit indirectly carotid intima media thickness, among the sarcoidosis patients with lung involvement.

Materials-Method

The research includes the patients who were diagnosed with sarcoidosis upon showing histopathologically "granulomatous inflammation without necrosis" and excluding mycobacterial infections after being bronchoscoped for diagnostical purposes on suspicion of sarcoidosis based on clinical and/or radiological findings in the Clinic of Chest Diseases of the Faculty of Medicine at Afyonkarahisar Health Sciences University from 01.08.2015 to 01.11.2021. All patients had isolated pulmonary involvement of sarcoidosis. Using the hospital electronic file system of the patients; Carotid intima media thickness values measured from the area 10 mm proximal to the bilateral common carotid artery bifurcation, which was previously recorded, were obtained by measuring at least 2 times by a single researcher with an ultrasound device belonging to the chest diseases clinic. Moreover, we have also received the hemogram data, biochemical parameters and the results of the respiratory function test of the patients, and have evaluated the radiological appearances of the patients. The patients have been radiologically divided into four groups according to the Siltzbach staging system:

Stage 1: Bilateral hilar adenopathy

Stage 2: Parenchymal infiltration with bilateral hilar adenopathy

Stage 3: Parenchymal infiltration without hilar adenopathy

Stage 4: Pulmonary fibrosis

We have compared the patients' demographic characteristics, hemogram and biochemical parameters, and carotid intima media thickness between these groups.

Statistical Analysis

We have employed Statistical Package for the Social Sciences for Windows Version 20.0 (SPSS Inc., Chicago, IL, ABD) in order to carry out the statistical analysis in the present study. We have used Kolmogorov-Smirnov test to evaluate the distribution of continuous variables. We express the categorical variables as number and percentage (N (%)). We have used chi-square test in order to compare the group rates. We express the normal distribution variables as average±standard deviation, and non-normal distribution variables as median (minimum-maximum). We have employed Student's *t*-test or Mann–Whitney *U* test for the comparison of the two groups in accordance with the distribution normality, and Pearson or Spearman correlation tests for the correlation analysis in accordance with the distribution normality. Statistical significance level has been determined to be $p<0.05$.

Ethıcs Commıttee Approval

Ethical approval for this study was obtained from The Faculty of Medicine Ethics Committee, Afyonkarahisar Health Sciences University (Number: 2022/11; Code: 2011-KAEK-2).

Results

Fourty eight sarcoidosis patients are included in the present study. Of the patients included in the study, 11 were male and 37 were female. There was no statistical difference between the groups in terms of Diabetes Mellitus and Hypertension (p value 0.324/0.615, respectively)

Table-1 shows the demographic, anthropometric and laboratory data, and the distribution of these data according to the stages.

The average age of the patients is 51,6 and the age has been found to be statistically significant between the stages **(p=0,002)**. (*Table-1*)

FVC: Forced Vital Capacity; FEV-1: Forced Expiratory Volume in a second; HDL: High Density Lipoprotein

CIMT: Carotid Artery Intima Media Thickness; LDL: Low Density Lipoprotein; TSH: Thyroid-Stimulating Hormone

Carotid intima media thickness has been measured 0,3mm (min.) and 1,3mm (max.). The average CIMT of the patients has been measured 0,66mm. It has been ascertained that the CIMT value increases in parallel with the stage increase. A statistically significant difference has been determined to exist among the carotid intima media thickness of the stages **(p<0,001)**.

The comparison of the carotid intima between the stages is shown in *Table-2*. The changes of carotid intima media thickness pursuant to the stages are shown in *Figure-1*.

In the correlation analysis; A weak positive correlation was found between CIMT and age (p=0.22 r=0.329). A stronger positive correlation was observed between stage and CIMT (p<0.001 r=0.562). The correlation analysis between CIMT and age, stage, triglyceride, LDL, and body mass index is shown in table 3.

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Table 1: The demographic, anthropometric and laboratory data of the investigational patients

	STAGE-1(n:21)	STAGE-2(n:15)	STAGE-3(n:9)	STAGE-4(n:3)	TOTAL(n:48)	p
AGE (Year)	45,9±11,29	50,47±10,72	59,11±9,89	67,67±8,50	51,6±12,25	**0,002**
HEIGHT (cm)	163± 8,55	161,67± 7,27	158,5± 4,33	166,67 ±7,63	161,98±7,53	0,338
WEIGHT (kg)	78,62±14,38	85,40±19,37	78,44±21,62	92,33±4,63	81,56±1727	0,43
T CHOLESTEROL (mg/dl)	188,92±43,21	184,81±44,80	185,28±43,02	204,60±52,74	187,93±92,99	0,90
TRIGLYCERIDE (mg/dl)	162,52±77,39	143,36±69,83	173,74±63,60	192,00±101,21	160,48±72,92	0,65
HDL (mg/dl)	54,91±27,14	49,92±9,98	55,03±10,21	55,30±3,99	53,40±19,16	0,87
LDL (mg/dl)	116,67±45,23	128,75±44,87	116,61±39,84	136,60±60,08	121,68±44,05	0,78
HGB (g/dl)	13,02±1,39	13,97±1,92	13,30±1,38	10,06±1,10	13,19±1,77	0,003
PLT (10^3u/L)	258,67±102,53	293,87±57,15	227,67±106,54	205,00±123,46	272,31±94,30	0,192
GLUCOSE (mg/dL)	117±24,81	113,65±33,03	199	141,00±45,25	126,76±36,42	0,15
CREATINE (mg/dl)	0,89±0,56	0,74±0,13	0,70±0,10	1,40±1,01	0,806±0,46	0,018
TSH (uIU/mL)	2,12±1,28	1,97±1,00	3,21±1,75	1,88±1,29	2,26±1,34	1,27
FEV-1 (litre)	2,23±0,56	2,25±0,68	1,60±0,53	1,58±1,12	2,08±0,67	0,39
FEV-C (litre)	2,68±0,75	2,75±0,74	1,73±0,64	1,90±1,60	2,48±0,87	0,11
CIMT (mm)	0,6±0,18	0,59±0,10	0,85±0,10	0,90±0,26	0,66±0,19	**0,000**

FVC: Forced Vital Capacity; FEV-1: Forced Expiratory Volume in a second; HDL: High Density Lipoprotein
CIMT: Carotid Artery Intima Media Thickness; LDL: Low Density Lipoprotein; TSH: Thyroid-Stimulating Hormone

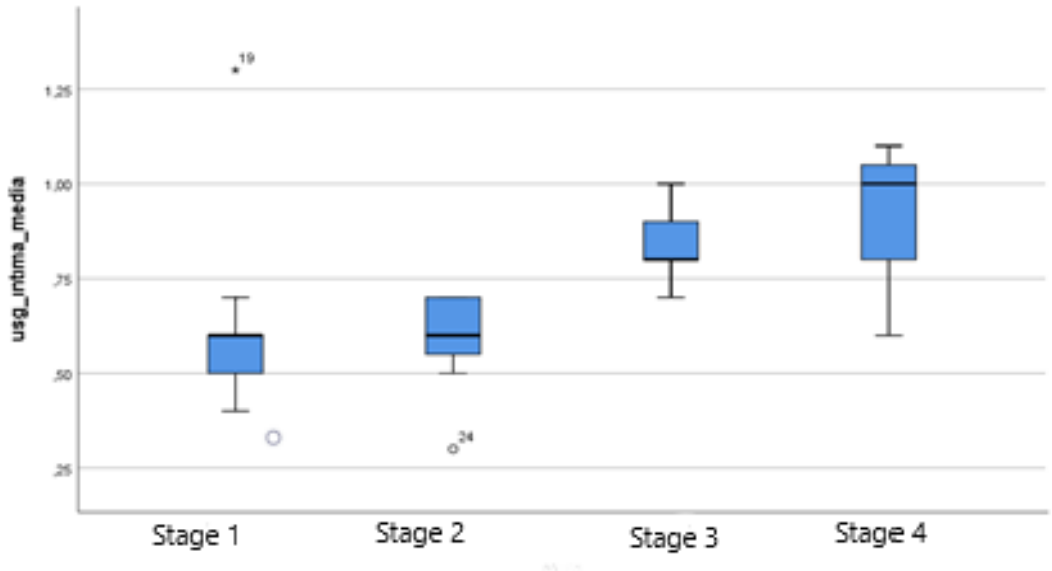

Figure 1: The changes of carotid intima media thickness pursuant to the stages

Table 2: The comparison of carotid intima media thickness between the stages

	STAGE-1(p)	STAGE-2(p)	STAGE-3(p)	STAGE-4(p)
STAGE-1(p)		0,99	**0,01**	**0,16**
STAGE-2(p)			**0,01,**	**0,17**
STAGE-3(p)				0,97

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Table 3: Correlation of Carotid Intima Media Thickness with Clinical Parameters

	p	r
Age	0,22	0,329
Stage	0,00	0,562
Triglyceride	0,250	0,169
Low Density Lipoprotein	0,93	0,245
Body mass index	0,831	0,32

Discussion

Atherosclerosis is a process that starts with the accumulation of inflammatory cells after endothelial dysfunction and subsequent accumulation of foamy fatty macrophages and the initiation of fatty streaks in the intima layer of the vessel. Afterwards, atherosclerotic plaques formed in the intima layer can be detected by ultrasound. In other words, increased carotid intima media thickness is one of the early indicators of atherosclerosis; used in clinical practice [8].

There have been studies in literature that evaluate the risk of atherosclerosis in the patients with sarcoidosis. Young et al. have shown that the risk of arterial induration and subclinical atherosclerosis increases in the patients with sarcoidosis [9]. Kul S. et al. have demonstrated that the coronary flow reserve of the patients with sarcoidosis may decrease in comparison with the healthy population so the risk of atherosclerosis may increase [10].

In addition, Bozkurt Yılmaz et al. have compared epidermal fat thickness and carotid intima media thickness between the sarcoidosis patients and control group. Consequently, the sarcoidosis patients' carotid intima media thickness has been found to be significantly greater than the control group's; it has also been concluded that the risk of subclinical atherosclerosis increases in the case of sarcoidosis [7].

The relation between sarcoidosis and atherosclerosis is likely to be associated with the inflammation which plays a similar role in both of their pathophysiologies. Inflammation in sarcoidosis emerges when alveolar macrophages activated by antigen and t-lymphocytes stimulate proinflammatory cytokines. At the end of this inflammatory cascade, the vascular structures get affected and endothelial dysfunction occurs. Endothelial dysfunction is an outset for atherosclerosis [11].

The increasing risk of atherosclerosis in the patients with sarcoidosis can be explained with the changes in lipid profile. Some researches have demonstrated that the patients with sarcoidosis experience changes in their lipid metabolisms, and their High Density Lipoprotein (HDL) levels decrease while their triglyceride levels increase [12]. The variation in lipid profile is a risk factor for atherosclerosis.

There have been almost no researches in the literature that suggest the relation between the pulmonary stage of sarcoidosis and atherosclerosis. Hence, we aim to evaluate the relation between the pulmonary stage of sarcoidosis and atherosclerosis. In our study, it was observed that CIMT increased as the lung involvement of sarcoidosis progressed ($p<0.001$). In the correlation analysis, a positive correlation was found between the stage and the thickness of the carotid intima media ($r=0.562$). There is a strong relationship between atherosclerosis and factors such as blood pressure, body mass index (BMI), blood triglyceride level and smoking [13]. In other words, these factors, independently of each other, can indirectly affect atherosclerosis and CIMT. In our study, there was no difference between the stages of BMI, triglyceride level and smoking.

In a study where Youn et al. evaluated CIMT in 433 healthy individuals aged between 40-70 years, it was found that CIMT correlated with age, high-low-density lipoprotein (LDL), increased BMI, and Diabetes Mellitus (DM)(14). In our study, there was no statistical difference between the stages in terms of LDL cholesterol level and DM. The atherosclerotic changes have a progressive course in time. They affect whole water vascular system including all coronary and carotid arteries over time. Beşir et al. have detected a positive relation between CIMT and age in research on 151 healthy individuals [15]. The present study also ascertains that age shows a significant difference between stages ($p=0,002$). The ages of the patients increase significantly from Stage-1 to Stage-4.

In our study, especially in stage-4 where pulmonary fibrosis is seen; There was a significant difference in CIMT according to stages 1 and 2. Stage 4 is pulmonary fibrosis and causes volume loss in the lung, and spontaneous recovery is not expected in these patients. Depending on the effect of secreted TGF-β and other cytokines, first inflammation and then fibrosis develops [1]. As it progresses towards stage 4, the increased risk of CIMT, that is indirectly atherosclerosis, may be associated with pulmonary fibrosis and increased inflammation. Our study still has certain constraints: the limited number of patients included in the research; the different number of patients among the stages; particularly, the limited number of advanced stage patients. Therefore, there is a serious need for researches which will be carried out in a multicentric way and with the participation of many more patients.

Ethical consent

The study was conducted according to the decision of the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee dated 07.01.2022 and numbered 2022/11.

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Conflict of interest

The authors below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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Author contributions

SA: Conceptualization, Writing - Original Draft, Writing - Review & Editing. **BA:** Formal analysis, Writing - Review & Editing. **EA:** Formal analysis, Writing - Review & Editing

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