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Original Article

The relationship of serum endocan levels and anti-TNF-alpha therapy in patients with ankylosing spondylitis

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Abstract

Objective: Endocan is a marker for vascular pathogenesis and important mediator of angiogenesis that strongly associates with inflammation and vascular diseases. Growing evidence suggest that inflammatory cytokine tumor necrosis factor (TNF-alpha) plays a role in its regulation and secretion, whereas TNF-alpha inhibitors may have the opposite influence. The aim of this research is to investigate the association between serum endocan and anti-TNF-alpha drug treatment in patients with ankylosing spondylitis (AS).

Methods: Serum endocan levels were analyzed in 42 patients with AS under anti-TNF-alpha usage. Control group consisted of 37 patients with AS who are not receiving anti-TNF drugs. Endocan is analyzed using ESM-1 ELISA kits. The blood glucose and lipid measurements of patients were also assessed.

Results: There was no significant change in serum endocan levels among groups. The total cholesterol, triglyceride, and LDL-C levels were higher in patients receiving anti-TNF-alpha; however, differences were not significant. There was no significant correlation between serum endocan levels and blood lipid measurements.

Conclusion: Anti-TNF-alpha treatment does not affect serum endocan levels in patients with AS. This research has been first to evaluate the relationship between serum endocan and anti-TNF-alpha therapy in AS. Future studies are necessary to verify the exact role of anti-TNF-alpha therapy on serum endocan levels in patients with AS.

Keywords: Anti-TNF-alpha treatment, ankylosing spondylitis, endocan

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Introduction

Endocan (endothelial cell-specific molecule-1/ESM-1) is a specific soluble glycoprotein secreted by human endothelial cells. It has a significant role in the development of blood vessels and is an indicator of vascular pathogenesis (1). Its relationship with vascular endothelial dysfunction and atherosclerosis was shown in recent studies (2-5). Inflammatory cytokines, just as tumor necrosis factor (TNF-alpha) and several interleukins, upregulate ESM-1 mRNA in a time-dependent manner and improve its secretion (6-8). In a recent study, patients with inflammatory bowel disease significantly had higher serum endocan levels than healthy subjects, and a close relationship was suggested between cytokine production and serum endocan levels (9).

Ankylosing spondylitis (AS) is a form of inflammatory arthritis that TNF-alpha plays a crucial role in the pathogenesis (10, 11). Accordingly, anti-TNF-alpha drugs have been used effectively for the treatment of AS (12). The influence of TNF-alpha on endocan upregulation is well described; however, it is not clear whether anti-TNF-alpha drugs interact with endocan to show their effect on inflammation and vascular endothelial function. Therefore, to clarify the role of endocan on the potential mechanisms of anti-TNF drugs, we conducted this study to examine serum endocan levels in patients with AS under anti-TNF treatment.

A series of changes in lipids and lipoproteins may occur in the course of disorders characterized by inflammation (13). There are increasing evidences to support the role of TNF-alpha that modulate both glucose and lipid metabolism. It has been shown that anti-TNF-alpha antibodies may protect against abnormalities in glucose and lipid metabolism; however, the mechanism underlying this relationship has not yet been explained (14). Total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C),

and triglyceride levels have been important biomarkers both in lipid metabolism and in cardiovascular dysfunction, as well as fasting glucose and HbA1c have been significant parameters in glucose metabolism (15, 16). Thereby, we also examined the effect of anti-TNF-alpha on these measurements, where we also correlated them with serum endocan.

Methods

This research was held at the Rheumatology Clinic of University Hospital as prospective, controlled clinical trial. The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Commission of the Medical Faculty. Patients written permission was taken before the study.

General assessments of patients

Patients (24-65 years old) diagnosed with AS, who were also examined by BASDAI standards, were included in the research. Participants were divided into two groups as anti-TNF (+) and anti-TNF (-). Patients under anti-TNF-alpha therapy for a minimum of three months were examined as the first group. Patients not using the anti-TNF drug but on non-steroid anti-inflammatory (NSAI) treatment were examined as the second group or control. Participants with the following criteria excluded in the study: any chronic illnesses other than AS, being under any steroidal or immunosuppressive drug treatment, pregnancy, and lactation. Demographic and clinical data of patients including body weight and height assessment were recorded in a database.

Serum endocan and biochemical measurements

To analyze the serum endocan and other biochemical parameters, two tubes (4 mL) of blood samples were collected in the morning, following an overnight fast. The first tubes centrifuged to separate serum from plasma. Serum samples kept in Eppendorf tubes in -70°C until the day of endocan analysis. Serum endocan levels (ng/mL) were analyzed using the Human ESM-1 ELISA Kit (Elabscience, China), based upon the company's protocol. The second tube was used to measure blood glucose and blood lipids.

Statistical analysis

Data are expressed as means (χ) and standard deviation (SD). Independent t test was used to evaluate the comparison of values between the groups. Pearson correlation (r) test was used to examine the relationship of endocan with biochemical parameters. A p-value less than 0.05 was considered statistically significant. The statistics were analyzed using the Statistical Package for Social Sciences (SPSS) server version 15.0 (SPSS Inc.; Chicago, IL, USA).

Results

The study comprised an overall 79 patients with AS. The first group included 42 patients (20 male, 22 female) under anti-TNF-alpha therapy. The second group included 37 patients (19 male, 18 female) under only NSAI treatment. The demographic and clinical data were similar in both groups as shown in Table 1. The mean BMI was over normal in both groups.

The mean endocan concentrations were, respectively, 0.901 and 0.804 ng/mL in groups receiving and not receiving anti-TNF-alpha therapy. The differentiation of the groups was not statistically important (p=0.812) (Figure 1).

The blood glucose and lipid measurements were also assessed in both groups and correlated with serum endocan levels. The total cholesterol, triglyceride, and LDL-C levels were higher in anti-TNF-alpha receiving patients; however, differences were not significant (p>0.05) (Table 2). Moreover, there was no significant correlation between serum endocan and blood measurements (p>0.05) (Table 3).

Discussion

Endocan is recognized as a specific molecule of the endothelium and has been shown to increase in some cases associated with inflammation. It is proposed as a risk factor for endothelial and cardiovascular dysfunction (17).

Normal circulating levels of endocan were found to be approximately 1.08 ng/mL, and it has been showed that the secretion of ESM-1 is significantly enhanced in the presence of TNF-alpha (5). In this study, it has been questioned whether there is an association between serum endocan levels and use of anti-TNF-alpha drugs. The mean endocan concentrations were found to be 0.901 and 0.804 ng/mL in patients receiving and not receiving anti-TNF-alpha respectively, which showed no significance (p>0.05). However, it has been suggested that the endocan parameter may correlate with the use of TNF inhibitors (9).

In inflammatory diseases, it has been estimated to examine higher serum endocan con-

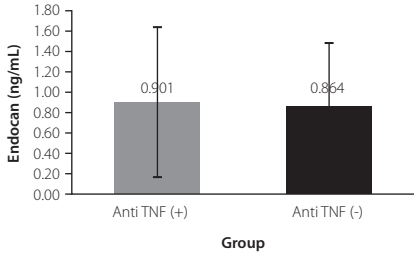


Figure 1. Mean serum endocan levels assessed between the patients' group based on receiving and not receiving anti-TNF-alpha therapy, error bars represent standard errors

Table 1. Demographic and clinical features of patient groups

	Anti-TNF (+)	Anti-TNF (-)
Patients (n)	42	37
Sex [male/female (n)]	20/22	19/18
Age (mean, min-max)	38.2 (24-54)	36.7 (20-57)
Education		
Primary, [n (%)]	10 (23.8)	11 (29.7)
High School, [n (%)]	26 (62)	14 (37.8)
University, [n (%)]	6 (14.2)	12 (32.5)
BASDAI*, [mean (SD)]	5.0 (1.11)	5.1 (1.23)
Anti-TNF- drugs		
Etarnercept, [n (%)]	10 (23.8)	-
Adalimumab, [n (%)]	11 (26.2)	-
Golimumab, [n (%)]	14 (33.3)	-
Infliximab, [n (%)]	7 (16.6)	-
Body measurements		
Height (cm)	166.0	170.0
Weight (kg)	75.6	78.4
BMI (kg/m^2)	27.4	27.1

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index (0-10, 10=worst); Anti-TNF (+): group receiving anti-TNF-alpha treatment; Anti-TNF (-): group not receiving anti-TNF-alpha treatment, but using non-steroid anti-inflammatory drug

Table 2. Blood lipid and glucose measurements in groups

	Anti-TNF (+)			Anti-TNF (-)				
	±SS	Min	Max	±SS	Min	Max	t	p
Fasting blood glucose (mg/dL)	93.8±1.99	72.0	134.0	93.3±2.28	74.0	144.0	0.091	0.853
HbA1c (%)	4.83±0.06	4.0	6.0	4.82±0.06	4.4	5.8	0.091	0.928
Triglyceride (mg/dL)	165.0±17.5	54.0	571.0	127.4±11.83	56.0	385.0	1.730	0.088
Total cholesterol (mg/dL)	196.1±5.44	117.0	273.0	184.9±6.13	128.0	294.0	1.365	0.176
LDL-C (mg/dL)	124.1±6.83	56.0	313.0	115.8±5.29	61.0	202.0	0.940	0.350
HDL-C (mg/dL)	46.7±2.00	25.0	88.8	48.4±1.86	32.0	96.0	-0.595	0.553

*p<0,05: Independent t test

Anti-TNF (+): group receiving anti-TNF-alpha treatment; Anti-TNF (-): group not receiving anti-TNF-alpha treatment, but using non-steroid anti-inflammatory drug; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol

Table 3. Correlation of serum endocan levels with blood lipid and glucose parameters

	Anti-TNF (+)				Anti-TNF (-)			
	Male (n: 20)		Female (n: 22)		Male (n: 19)		Female (n: 18)	
	r	p	r	p	r	p	r	p
Fasting blood glucose (mg/dL)	-0.102	0.961	-0.296	0.182	-0.265	0.272	-0.080	0.740
HbA1c (%)	-0.051	0.831	-0.170	0.450	-0.039	0.875	-0.112	0.658
Triglyceride (mg/dL)	-0.102	0.670	0.292	0.187	-0.261	0.280	-0.160	0.524
Total cholesterol (mg/dL)	0.078	0.744	0.007	0.975	0.070	0.774	-0.090	0.720
LDL-C (mg/dL)	0.032	0.892	0.094	0.678	-0.122	0.618	0.050	0.843
HDL-C (mg/dL)	0.206	0.383	0.121	0.592	0.383	0.105	0.142	0.573

*p<0,05: Pearson correlation

Anti-TNF (+): group receiving anti-TNF-alpha treatment; Anti-TNF (-): group not receiving anti-TNF-alpha treatment, but using non-steroid anti-inflammatory drug; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol

centrations because of the increased levels of TNF-alpha (5). Sarrazin et al. suggested that inflammatory cytokines just as TNF-alpha and pro-angiogenic factors strongly induced the secretion of ESM-1 (3). Thereby, in this study, we expected to find lower serum endocan levels in AS patients receiving anti-TNF-alpha therapy, due to a possible decrease in TNF-alpha levels. Unfortunately, the data presented here showed no correlation between anti-TNF-alpha therapy and endocan concentration. On the contrary, a cohort study developed on pediatric renal transplant patients showed significantly higher endocan levels (12.2 ng/mL) that correlated with the increased levels of TNF-alpha; however, no association was found between age, gender, and disease activity. Moreover, endocan levels were not changed after receiving immunosuppressive and antihypertensive agents (18). It has been showed that serum endocan levels in subjects with chronic kidney diseases in the first (1.2 ng/mL) and second quartiles (2.8 ng/mL) were significantly lower than those of the third (6.6 ng/mL) and fourth quartiles (13.3 ng/mL), pointing out that TNF-alpha levels were expected to be higher in later stages (19). However, in our study, mean endocan levels were found to be lower than the literature in both study groups (Figure 1).

In this research, we also examined blood measurements, but we found no substantial correlation between serum endocan and blood lipids (p>0.05) (Table 3). Even though differences were not important (p>0.05) (Table 2), the interesting thing was that total cholesterol, triglyceride, and LDL-C levels were higher in anti-TNF-alpha receiving patients whereas we expected just the opposite results. Unlike our study, it has been showed that in HT patients, serum endocan levels notably and independently correlated with the existence of coronary disease and change in blood lipids when compared with healthy individuals (2). Additionally, anti-TNF-alpha therapies have showed particularly improved endothelial function together with regulated blood lipids (20).

Endocan levels also found to be positively correlated with glucose levels in patients with admission hyperglycemia and acute myocardial infarction (21). In our analysis, there was no relationship between glucose regulation and endocan levels. This may be related to the fact that we excluded subjects with prediabetes and diabetes from the study.

Our study has some limitations. We could not make a power analysis to calculate the minimum sample size, since this was the first study investigating the importance of endocan in patients with AS. The patients were not paired for their endocan levels before and after the treatment, but instead, we investigated independent patient groups.

In conclusion, serum endocan solely may not inform types of illnesses; however, its recognition over the normal range and relationship with biological drug therapies may provide a clue to investigate for several important diseases (chronic inflammatory diseases, vascular diseases, etc.). Although our results were not significant among the groups, this research is important to be the first one evaluating the relationship between serum endocan and anti-TNF-alpha therapy. Further studies are necessary to show the effect of serum endocan and its relationship with TNF-alpha inhibitors.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University School of Medicine.

Informed Consent: Written informed consent was obtained from who participated in this study.

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