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Title: The evaluation of serum biomarkers in patients with sarcoidosis: Can visfatin be a new biomarker for sarcoidosis?

Short title: Evaluation of Visfatin As A Novel Biomarker of Sarcoidosis

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ABSTRACT

Objective: Sarcoidosis is a chronic systemic inflammatory disease which can affect multiple organ systems. The role of biomarkers in the diagnosis and prognosis of sarcoidosis is increasing. Interest in the role of adipose tissue mediated inflammation in the pathogenesis of the inflammatory diseases has increased in recent years. Visfatin is a proinflammatory adipocytokine which has been studied for several inflammatory diseases such as diabetes mellitus, obesity and metabolic syndrome. Our aim is to assess serum visfatin levels in sarcoidosis and its relation with other markers of inflammation (CRP, ACE and ESR).

Material and Methods: We enrolled 59 patients with sarcoidosis and 21 healthy controls. We measured plasma levels of visfatin along with serum CRP, ESR, ACE using ELISA (enzyme-linked immunosorbent assay) kits (Blue Gene Biotech, Shanghai, China).

Results: Visfatin levels were not significantly different between patients and control subjects (29.9±15.8 ng/ml for patients and 23.93±16.73 ng/ml for controls, p=0.15) and there was no correlation between visfatin and serum CRP, ACE or ESR in patients with sarcoidosis.

Conclusion: Visfatin recently is being discussed as biomarker for inflammatory diseases in several studies and results are controversial. In our study, no differences were found in serum level of visfatin between patients with sarcoidosis and control group.

KEY WORDS: sarcoidosis; biomarkers; visfatin; inflammation

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INTRODUCTION

Sarcoidosis is a multi-system disorder with a predilection to affect the lungs. Spontaneous remission often occurs, although approximately one-third of cases go on to develop chronic disease, that may be fatal [1,2]. The etiology of sarcoidosis is yet to be fully understood. However, immunologic evidence and the geographical variation of the disease have suggested various causes including infection, occupational exposure, and genetic factors [3]. Although the mechanisms are yet to be defined, a chronic inflammatory state is thought to produce pathophysiological effects, resulting in non-caseating granuloma formation in the lungs and other systems [4]. Despite several known gene associations, there is a lack of clinically useful biomarkers [5].

Adipokines are proteins originating from adipose tissue and macrophages and they regulate the inflammatory response in many chronic inflammatory disorders [6]. Visfatin is a pro-inflammatory adipokine previously named pre-B cell colony-enhancing factor [7]. It is limiting enzyme in nicotinamid adenine dinucleotide (NAD) synthesis and as such known as nicotinamid phosphoribosyl transferase (NAMPT) [8]. Visfatin has been proposed as a new marker of inflammation in diabetes mellitus (DM), metabolic syndrome, polycystic ovary syndrome, coronary artery disease, and rheumatoid arthritis (RA) [9–13]. Visfatin was shown to induce the secretion of proinflammatory cytokines including TNF-α, IL-6 and IL-8,while these cytokins could induce the expression of visfatin [14]. In sarcoidosis pathogenesis, the recognition of the antigen by CD4 positive T lymphocytes is a critical step in triggering the disease. During the inflammatory process, production of cytokines such as TNF-α, INF-10, IL-2, TGF-β, IL-8, IL-12, IL-10 and IL-23 increases [15]. The presence of common inflammatory pathways suggests that visfatin should play a role in the pathogenesis of sarcoidosis. The relationship between sarcoidosis and visfatin has not been previously reported in the literature. We aimed to assess visfatin levels in sarcoidosis patients, and to evaluate the relationship between

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this visfatin concentration and angiotensin converting enzyme (ACE), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lung function tests, and the stage of sarcoidosis.

MATERIALS AND METHODS

Fifty nine patients with sarcoidosis and twenty one healthy controls admitted to outpatient clinic of our hospital were involved in our study between May 2015 and January 2016. Patients with diabetes mellitus and those having a body mass index over 25 kg/m^2 were excluded. For each patient, routine tests such as posteroanterior chest radiography, complete blood count (CBC), serum ACE levels, lung function tests were performed. In addition, sample of venous blood was obtained from each subject for analysis of visfatin. After centrifugation at 3000 rpm for 10 minutes, supernatant was stored at -20^0C. Serum concentrations of visfatin were analyzed by ELISA kits (Blue Gene Biotech, Shanghai, China). Our study complied with the ethical principles of the Helsinki Declaration. All participating subjects gave informed consent. Our study was approved by the Ethical Committee of Clinical Research.

Statistical analysis:

Data were analysed with the Statistical Package for Social Sciences (SPSS) version 22.0 for Windows software (IBM SPSS Statistics Data Editor). Descriptive data were given as number of participants and frequency. Categorical variables were expressed as the number of patients and the visfatin percentage value. Comparison of categorical variables were performed with Chi-square and Fisher's exact tests. Continuous variables were documented as mean and standard deviation and the Shapiro-Wilk test was

used to determine whether these variables were normally distributed. The Student's t-test and Mann-Whitney U test were used for continuous varaiables depending on the normality of their distribution. Spearman's correlation test was used to analyse the relationship between variables. A p-value of <0.05 was considered statistically significant.

According to previous studies with visfatin, in order to find a significant difference of 10ng/ml between groups with the power of 0.80, the smallest sample size must be 16 patients for each group. In our study, we included 21 controls and 59 patients with sarcoidosis and the power of our study was 0.90.

RESULTS

The sarcoidosis group consisted of 48 female (81.4%) and 11 male (18.6%) patients with mean age of 46.33± 12.78 years. Depending on the radiological findings, 11 (18.6 %) of these cases were considered to be in stage 1, 47 (79.7%) were in stage 2, and 1 (1.7%) was in stage 3. Average serum ACE level was 69.2±52.3 U/L. Erythrocyte sedimentation rate (ESR) was 25.70±16.45 mm/hr, visfatin level was 29.9±15.8 ng/ml. Patient characteristics are summarized in Table 1.

In the control group, there were 8 females (38%) and 13 male (62%) patients and had a similar mean age with the sarcoidosis group (46.33±12.78 and 41±9, respectively, p=0,07)

Levels of visfatin did not differ significantly between patients with sarcoidosis and the control group (29.9±15.8 ng/ml and 23.93±16.73 ng/ml, p=0,15). CRP (7,09±7,72 mg/L for sarcoidosis and 2,17±1,62 mg/L for control, p<0,001) and ESR levels (25,7±16,45 mm/hr for sarcoidosis and 11,26±8,97 mm/hr for control, p<0,001) were higher in the sarcoidosis group than the controls. We also evaluated sarcoidosis patients in two groups according to parenchymal involvement, and found no significant difference in their serum visfatin levels (30±15.51 ng/ml and 28.9±17.64 ng/ml, respectively; p= 0,826). Patients with parenchymal involvement had higher serum ACE level and ESR compared to patients without parenchymal involvement (p=0,002 and p=0,043, respectively). FEV1 (lt), FVC (lt) and DLCO

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(ml/mmHg/min) were lower in parenchymal involvement but there was no statistical significance (Table 2).

Similarly, sarcoidosis patients with high-ACE levels (>52 U/L; over the limits of normal) had significantly higher ESR values (30,1±17,5 vs 19,9±13,1, p=0,019). Levels of ACE and ESR had a positive correlation (p=0,03 and r=0,274), and also between serum levels of ACE and C reactive protein (CRP) (p=0,013 and r=0,325). (Table 3).

A comparison of the visfatin and ACE levels according to previous steroid use or being steroid naive showed no statistical significance (p=0,346 for visfatin; p= 0,532 for ACE). Evaluation of visfatin and ACE levels for steroid naive patients and patients on current steroid treatment showed no statistical difference (p=0,721 for visfatin; p= 0,627 for ACE).

DISCUSSION

Serum visfatin levels did not differ significantly between patients and controls, or between patients with or without parenchymal involvement. Additionally, no correlation was detected between the serum visfatin level and other inflammatory markers such as ACE, ESR, or CRP.

Visfatin is a proinflammatory adipokine involved in inflammation, and the upregulation of this adipokine leads to the development of a chronic low-grade inflammatory state. This biomarker has been studied for several inflammatory diseases such as obesity, metabolic syndrome, type 2 DM, polycystic ovary syndrome, and RA, but the findings are controversial [10-13, 16-18]. Subsequent studies described visfatin upregulation in several immune cells including monocytes, lymphocytes, dendritic cells and macrophages [19–21]. Visfatin was shown to activate pro-inflammatory pathways and induce other proinflammatory cytokines including TNF-α, IL-1β and IL-6. Noteworthy high visfatin levels were detected in overweight/obese patients, whereas weight loss induced by both physical exercise and bariatric surgery lowered the circulating levels of visfatin [22]. Similarly, a strong clinical

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association has been demonstrated between visfatin and type 2 DM, independent of BMI [23–25]. El-Suhaimi et al. suggested that an increased, decreased, or unchanged level of visfatin-induced endothelial angiogenesis is mediated by the VEGF, MMP, MAPK, and PI3K/Akt signalling pathways [17]. Syrbe et al. reported higher visfatin levels in ankylosing spondylitis (AS) patients than controls, with elevated levels predicting the relative to baseline levels predict the subsequent progression of radiographic damage [26]. In another study, asthmatic patients were found to have significantly higher serum visfatin levels than controls [6]. Another conditions associated with high basal serum visfatin levels was inflammatory bowel disease [27]. Additionally, a strong correlation has been reported between visfatin and inflammatory markers, such as CRP and IL-6 [22,28]. However, visfatin levels were not significantly different between patients and controls in our study. We also detected no correlation between the serum visfatin level and other inflammatory markers such as ESR or CRP. Similar to us, Celap et al. reported that visfatin was not associated with inflammatory markers such as CRP in hemodialysis patients [29]. In a study evaluating the correlation of elevated serum visfatin levels and inflammatory markers (hs-CRP, IL-6, TNF-α, waist circumference, TG, and BMI) in obese children, visfatin was only correlated with BMI and IL-6; no significant correlation with hs-CRP was observed [30]. Similarly, serum visfatin levels, CRP and sedimentation rate showed no correlation in patients with chronic viral hepatitis B and metabolic syndrome [31,32]. We found no statistical difference in visfatin levels between steroid-naive patients and patients currently receiving steroid treatment. Our results suggest that inflammatory pathways are present in sarcoidosis pathophysiology, but that visfatin is not increased. The general role of visfatin in inflammatory diseases is still unclear because studies have shown inconsisted results.

Under different conditions including metabolic syndrome, type 2 DM, rheumatic disease, and hemodialysis, visfatin had a positive correlation with the presence and severity of the disease [33,34]. Circulating visfatin levels and disease activity had similar correlation in patients with RA [35]. In the

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present study, we found no significant difference respecting visfatin levels between groups with or without parenchymal involvement or stages. Patients with pulmonary involvement had significantly higher serum ACE levels and ESR. We found no association between CRP levels and parenchymal involvement. Our findings support those of Dirican et al. [36]. Based on the results, we suggest that the severity of disease may be associated with the serum ACE level and ESR rather than CRP.

Our study had several limitations. First, the number of patients was limited as it was a single center study. Cohort studies having larger sample sizes are needed to investigate this possibility. Second, because our study was cross-sectional, we only evaluated and compared one sample of blood taken at a single visit for visfatin for all patients with different durations of sarcoidosis. Periodic serum visfatin level monitoring during follow-up with newly diagnosed patients with sarcoidosis might yield different results. Having more data from the same person could also make it possible to calculate a base level for visfatin and study the use of visfatin as a biomarker for changes in inflammation. Third, we did not exclude patients with hypertension. However, Dogru et al reported that visfatin plasma levels were not correlated with blood pressure in patients with uncomplicated hypertension and that adipokine dysregulation does not seem to have a role in new-onset hypertension [37]. Also, we included patients receiving steroid treatment. However, previous studies have reported that visfatin levels were not affected by systemic glucocorticoid treatment [38,39]. We also found that serum visfatin levels were similar between groups receiving current or previous steroid treatment. Even though various studies have not demonstrated a relationship between visfatin and steroid use or hypertension, future studies should still take into account that proinflammatory pathways can be affected.

In conclusion, our study that was the first to evaluate serum visfatin levels of sarcoidosis patients. We found no convincing evidence to indicate the use of visfatin as a biomarker for sarcoidosis. In order to better elucidate the role played by visfatin in chronic inflammatory disorders such as sarcoidosis, large prospective cohort studies will be required.

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Table 1. Characteristics of the patients with sarcoidosis	
Number of patients	59
Age, years (mean ± SD)	46.33 ± 12.78
Female /Male	48/11
Stage of disease 0 (n) 1 (n) 2 (n) 3 (n) 4 (n)	 0 11 47 1 0
Follow-up period (months)	27.7 ± 32.3
Steroid treatment (over all) (n)	20/59
Steroid treatment (current) (n)	5/59
Steroid naive patients (n)	39/59

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Table 2. Comparison of sarcoidosis patients with/without parenchymal involvement			
	With parenchymal involvement	Without parenchymal involvement	P
Age (years)	46.27 ± 12.79	46.6 ± 13.38	0.933
CRP (mg/l)	7.62±8.28	4.81 ±4.11	0.282
Sedimentation (mm/hr)	27.08 ±17.67	19.81 ±7.69	0.043
Serum ACE level (U/L)	75.91 ± 54.84	39.95 ± 23.92	0.002
Serum visfatin level (ng/ml)	30 ± 15.51	28.90 ± 17.64	0.826
FEV1 (lt)	2.51 ± 0.79	2.69±0.74	0.507
FEV1 (%)	92.59 ± 13.91	102.66 ±26.5	0. 249
FVC (lt)	3.05 ± 0.95	3.40± 0.81	0.260
FVC (%)	92.68 ± 18.12	109.03 ± 25.83	0.070
DLCO (ml/mmHg/min)	20.76 ± 7.30	21.31 ± 6.4	0.863

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Table 3. Correlation between biomarkers				
	ACE	ESR	CRP	Visfatin
ACE p		0.03	0.013	>0.99
r		0.274	0.325	<0.001
Visfatin p	> 0.99	0.42	0.30	
r	< 0.001	-0.109	-0.137	

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