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Egyptian Rheumatology and Rehabilitation (2023) 50:28
https://doi.org/10.1186/s43166-023-00196-8

Egyptian Rheumatology and Rehabilitation

RESEARCH Open Access

Relationship between galectin-3 level and disease activity in ankylosing spondylitis patients

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Abstract

Background and aims Ankylosing spondylitis (AS) is a chronic inflammatory disease that chiefly affects the sacroiliac joints and the spine. Galectin-3, a chimera-type member of the galectin family, binds glycoconjugates containing N-acetyllactosamine. Galectins play a role in regulation of embryogenesis, angiogenesis, neurogenesis, and immunity. The aim of the present study was to evaluate the serum galectin-3 level and its possible association with disease activity in AS patients. Forty five AS patients and 35 healthy controls enrolled in this study. All participants with a history of hyperlipidemia, liver, renal, hematological, familial thyroid, neoplastic, autoimmune infectious diseases and using anti-inflammatory drugs were excluded from the study. Serum galectin-3 levels concentration was measured using a commercial chemiluminescent microparticle immunoassay. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were measured. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score–CRP (ASDAS-CRP) were used to evaluate disease activity in AS patients.

Results Serum galectin-3 levels were significantly higher in AS patients compared to the control group ($p=0.04$). A correlation was determined between the serum galectin-3 levels and BASDAI and ASDAS-CRP scores in the AS patients ($r=0.49$, $p<0.001$; $r=0.56$, $p<0.001$, respectively). In AS patients, serum galectin-3 levels were significantly related with CRP levels but were not related with ESR ($r=0.57$, $p<0.001$; $r=0.25$, $p=0.09$, respectively).

Conclusions The serum galectin-3 levels were higher in AS patients and were correlated with disease activity. This study may be useful to reveal the role of galectin-3 in inflammation and to evaluate disease activity in AS patients.

Keywords Ankylosing spondylitis, Disease activity, Galectin-3, Inflammation

Background

The sacroiliac joints and the spine are affected primarily by ankylosing spondylitis (AS) known as a chronic inflammatory disease. It is a disease that can lead to a decrease in the quality of life together with structural and functional disability. The etiopathogenesis of AS is not known exactly. It is thought that the relationship between human leukocyte antigen (HLA)-B27 antigen and disease develops as a consequence of the immunological response to triggering environmental factors in people with a genetic predisposition [1, 2]. AS is characterized by changes in T cell function [3]. The secreting of tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 pro-inflammatory cytokines play an important role in the systemic inflammatory response progress [4]. The previous studies have shown that TNF and IL-6 levels are high in AS patients and associated with disease activity [5, 6].

Galectins have a significant role in embryogenesis, angiogenesis, neurogenesis, and immunity regulations.

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Their levels of expression and secretion are changed during tumorigenesis, neurodegeneration, and inflammation [7]. Galectin-3, a galectin with chimera type, binds glycoconjugates that contain N-acetyllactosamine [8]. In tissues such as the skeleton, kidneys, brain, and gut, it was demonstrated to be broadly expressed [9]. Studies have demonstrated that galectin-3 mainly triggers or amplifies inflammatory responses by promoting immune cell activation, migration, and pro-inflammatory cytokine secretion, or by suppressing T cell apoptosis [10]. Galectin-3 has been demonstrated to support the production of Th17 cells in studies of autoimmune diseases in which Th17 cells are effective in inflammation [11]. It has been shown that the production of T cells and the serum levels of TNF-α, IL-17, and IL-6 are decreased in galectin-3 deficient mice [12]. Wang et al. [13] found that galectin-3 was more produced in the synovium of collagen-induced arthritic rats, compared with the control group. Overall, these findings show that galectin-3 may have an effective role in inflammation and plays an important role in serum levels of TNF and IL-6, which are effective in disease activity of ankylosing spondylitis. Few studies have been conducted in the literature investigating the effect of galectin-3 in ankylosing spondylitis [14]. We aimed to evaluate the serum galectin-3 level and its possible association with disease activity in AS patients in our study.

Methods

The study was carried out as a cross-sectional study. Forty-five patients (17 females, 28 males) diagnosed with AS according to the modified New York criteria [15], and 35 healthy volunteer hospital staff (15 females, 20 males) were included in our study. Detailed histories of all participants were obtained, and systemic and rheumatologic examinations were performed. Demographic, clinical and laboratory measurements of AS patients were performed and compared with the control group. We excluded all participants who had a history of hyperlipidemia, liver, renal, hematological, familial thyroid, neoplastic, autoimmune infectious diseases, and receiving anti-inflammatory drugs. From each of the participants, a written informed consent was taken and this research was ratified by the local ethics committee of our institution (2016-85/102).

Laboratory measurements

Serum galectin-3 concentration was measured using a commercial chemiluminescent microparticle immunoassay (CMIA) kit for human galectin-3 (Architect, Abbott Diagnostics, Germany) according to the manufacturer's instructions on Abbott Architect 12000SR autoanalyzer. The limit of blank, the limit of detection, and the limit of quantitation were determined by the manufacturer to be 0.80 ng/mL, 1 ng/mL, and 4 ng/mL, respectively. The linearity range for human galectin-3 was between 4 ng/mL and 114 ng/mL (in the way determined by the manufacturer). The maximal intra-assay coefficient of galectin-3 variation was 6.7% at 95.7 ng/mL mean concentration, as determined by the manufacturer. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels of the patient and control groups were measured.

Clinical measurements

For the assessment of disease activity, the Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were utilized in patient group. BASDAI is a scale consisting of 6 questions with 5 basic disease symptoms (0: no activity and 10: the highest level of activity). Calculation in ASDAS-CRP was made with questions 2, 3, and 6 in the BASDAI questionnaire, global assessment of the patient, and CRP values. The Turkish versions of BASDAI and ASDAS-CRP which underwent validity and reliability test were used [16, 17].

Statistical analysis

The SPSS version 21.0 program (SPSS, Inc., Chicago, IL, USA) was utilized to evaluate the statistical data. Kolmogorov-Smirnov test is used for the conformity of continuous variables with normal distribution. All the variables were determined to be normally distributed. Data of the study were shown as mean ± standard deviation. In order to compare the measurement values of the AS patients and control group, the Student t test was used. Pearson correlation coefficients were calculated to assess the relationship between the outcomes in AS patients. Simple linear regression analysis was utilized to evaluate the relation between serum galectin-3 and BASDAI index in AS patients. The values of $p < 0.05$ were considered as statistically significant.

Results

Forty-five AS patients and 35 healthy controls enrolled in this study. The mean age of the patient group and control group were 40.75 ± 11.67 years and 38.68 ± 8.56 years, respectively. The demographic, clinical, and laboratory characteristics of the AS patients and control group are presented in Table 1. There were no statistically significant differences in age, gender and BMI in the AS patients group compared to the control group ($p = 0.38$, $p = 0.64$, $p = 0.38$, respectively). Serum galectin-3, CRP, and ESR levels were significantly elevated in the AS patients compared to the control group ($p = 0.04$, $p < 0.001$, $p < 0.001$, respectively). We did not find statistically significant differences between serum galectin-3 levels in HLA-B27 positive and negative patients ($p = 0.79$). There was no

Table 1 Comparison of the demographic, clinical and laboratory measurements in the study groups

Variables	Patient group ($n=45$)	Control group ($n=35$)	*P* values
Age (years), mean ± SD	40.75 ± 11.67	38.68 ± 8.56	0.38
Gender (female/male), *n* (%)	17/28 (37.77/62.22)	15/20 (33.33/44.44)	0.64
BMI (kg/m^2), mean ± SD	27.34 ± 2.57	26.79 ± 3.03	0.38
Disease duration (years), mean ± SD	7.44 ± 4.00		
History of peripheral arthritis, *n* (%)	9 (20)		
History of uveitis, *n* (%)	6 (13.33)		
HLA-B27 positivity, *n* (%)	37 (82.22)		
Galectin-3 (ng/mL), mean ± SD	15.79 ± 5.17	13.72 ± 3.54	0.04
CRP (mg/dL), mean ± SD	1.55 ± 0.97	0.64 ± 0.34	< 0.001
ESR (mm/h), mean ± SD	21.80 ± 9.49	12.97 ± 2.53	< 0.001
BASDAI ± SD	2.63 ± 0.99		
ASDAS-CRP ± SD	1.60 ± 0.56		
NSAID, *n* (%)	9 (20)		
INF, *n* (%)	11 (24.44)		
ETN, *n* (%)	6 (13.33)		
ADA, *n* (%)	14 (31.11)		
GOL, *n* (%)	5 (11.11)		

BMI Body mass index, *SD* Standard deviation, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *CRP* C-reactive protein, *ASDAS-CRP* Ankylosing Spondylitis Disease Activity Score-CRP, *ESR* erythrocyte sedimentation rate, *NSAID* Non-steroidal anti-inflammatory drugs, *INF* Infliximab, *ETN* Etanercept, *ADA* Adalimumab, *GOL* Golimumab

Table 2 Relationship between serum galectin-3 levels and other variables in AS patients

	CRP (mg/dl)	ESR (mm/h)	BASDAI	ASDAS-CRP	Disease duration (years)
Galectin-3 (ng/mL)					
r	0.57	0.25	0.49	0.56	−0.03
p	< 0.001	0.09	< 0.001	< 0.001	0.81

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *ESR* Erythrocyte sedimentation rate, *CRP* C-reactive protein, *ASDAS-CRP* Ankylosing Spondylitis Disease Activity Score-CRP, *AS* Ankylosing spondylitis

statistically significant difference between serum galectin-3 levels and radiographic progression ($p = 0.09$). In AS patients, the serum galectin-3 levels were related with CRP levels but were not related with ESR levels ($r = 0.57$, $p < 0.001$; $r = 0.25$, $p = 0.09$, respectively) (Table 2). The serum galectin-3 levels in AS patients were related with BASDAI scores ($r = 0.49$, $p < 0.001$) (Fig. 1). The serum galectin-3 levels in AS patients were correlated with ASDAS-CRP ($r = 0.56$, $p < 0.001$).

Discussion

The present study showed that serum gal-3 levels were higher in AS patients than in healthy subjects. Also, serum galectin-3 levels were associated with disease activity in AS patients. IL-17 producing proinflammatory mediators (like TNF-α, IL-1, IL-6) contribute to various aspects of acute inflammation [18]. The release of proinflammatory cytokines like TNF-α and IL-6 has an important role in the development of the systemic inflammatory response [4]. TNF-α, a significant signaling component of the immune system and proinflammatory molecule, exists at higher concentration in AS [19]. In recent years, many studies have been conducted to investigate the effect of galectin-3 on inflammation [11–13, 20, 21]. In animal experiments of autoimmune disease, galectin-3 increases IL-17 and Th17 which has a significant effect on inflammation production. Jiang et al. [20] suggested that lower levels of IL-17 existed in galectin-3 deficient mice with the alleviated experimental autoimmune encephalomyelitis symptoms. Wang et al. [13] stated that when it was compared to control subjects, galectin-3 was high in the synovium of collagen induced arthritic rats. Jeon et al. [21] found that treatment with galectin-3 significantly induced the transcription of varied proinflammatory mediators including IL-6, IL-1β proteins, and TNF-α. They demonstrated the enhanced production of IL-12 proteins, IL-1β, and TNF-α in galectin 3-treated microglia and did not detect any change in levels of the IL-10 protein. Forsman et al. [12] reported that inflammation was suppressed, and proinflammatory cytokine (IL-17-producing T cells, TNF-α, and IL-6) levels decreased in galectin-3 deficient mice. The triggering role of galectin-3 in arthritis was verified by this study. In the study by Filer et al. [11] showed that when exogenous recombinant galectin-3 was administered in rats

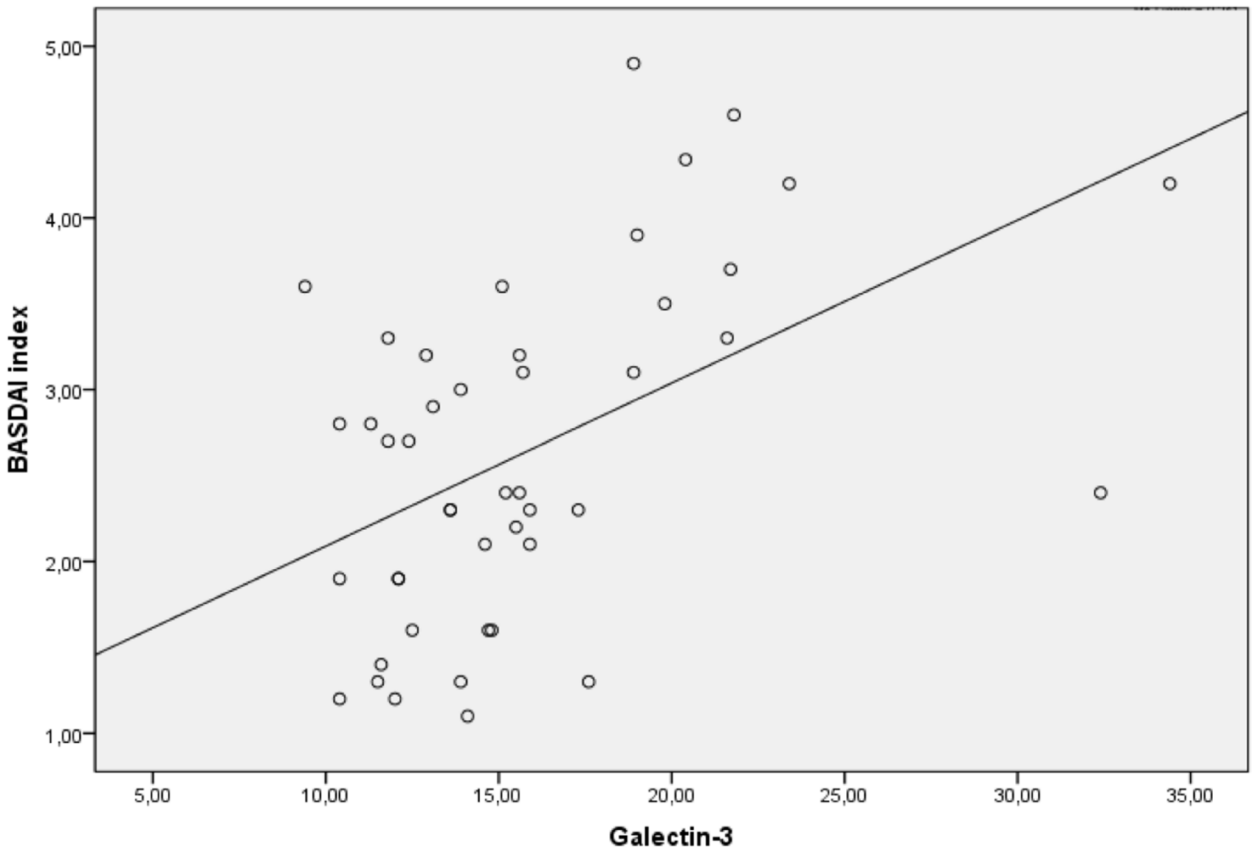

Fig. 1 Correlation between serum galectin-3 levels and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in patients with ankylosing spondylitis

with experimental RA, proinflammatory cytokines such as TNF-α, IL-6 were secreted in synovial fibroblasts.

The pathogenesis of different inflammatory diseases and the function of immune cells are affected by galectin-3. Galectin-3 plays a role pro-antiinflammatory processes depending on diverse factors including its intracellular or extracellular localization and the target cell implicated in these processes [22]. In previous studies, it has been shown that galectin-3 levels are elevated in the serum of patients with inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, Behçet's disease, and systemic sclerosis [23–26]. Furthermore, Gruszewska et al. [27] reported that serum galectin-3 concentration is elevated in rheumatoid arthritis (RA), systemic sclerosis (SSc), and systemic lupus erythematosus and galectin-3 could be a laboratory marker with high diagnostic power for the diagnosis of RA and SSc. Bhattacharjee et al. [28] demonstrated that galectin-3 binding protein was to be overexpressed 4-fold in spondyloarthritis than rheumatoid arthritis. In the research carried out by Ohshima et al. [23], it was indicated that in the course of inflammatory flares in rheumatoid arthritis, galectin-3 existed greatly in synovial tissue. Serum galectin-3 levels were significantly higher in AS patients compared to the control group in this study. The results of our study were consistent with the other studies. We thought that an increase in serum galectin-3 level may contribute to the inflammatory process in AS.

Forsman et al. [12] showed that galectin-3 had a pathogenic role in the development and progression of arthritis and the systemic levels of IL-6, the frequency of IL-17-producing cells, and TNF-α accompanied that disease severity by alterations. They reported in a study on mice with antigen-induced arthritis that a very important decrease in joint erosion and synovitis were observed in galectin-3-deficient mice compared to wild type mice. The serum concentration of CRP is accepted as an indicator of inflammatory activity in the body. The use of inflammatory markers such as CRP has been recommended by the Assessment of SpondyloArthritis international Society [29]. The serum concentration of CRP was significantly increased in AS patients compared to the control group in the present study. There was also a significant relation between serum galectin

levels and serum concentration of CRP. There are many studies in the literature showing that galectin-3 is effective on inflammation. Cao et al. [14] reported that serum galectin levels were high in AS patients and associated with disease activity and CRP levels. Chen et al. also suggested that there is a positive correlation between serum galectin-3levels and disease activity in adult-onset Still's disease [30]. We also observed that serum galectin-3 levels were related to disease activity in AS patients in our study. These results may be due to the effect of galectin-3 on inflammation.

Study limitations

This study has some limitations. As it was a single-center study, the number of participants in our study was small. We did not evaluate the effects of drugs such as NSAIDs and anti-TNF on serum galectin-3 levels. The prognostic value of galectin-3, its relationship with comorbid diseases in ankylosing spondylitis, and its role in monitoring treatment in ankylosing spondylitis may be discussed in future studies.

Conclusions

The results of this study indicated that serum galectin-3 levels were increased in AS patients, and they were associated with disease activity. Serum galectin-3 may have a significant effect on inflammation in AS patients. This study may help to reveal the role of galectin-3 in inflammation and contribute to the growing literature in this area.

Abbreviations

AS	Ankylosing spondylitis
HLA	Human leukocyte antigen
TNF- α	Tumor necrosis factor-alpha
IL	Interleukin
CMIA	Chemiluminescent microparticle immunoassay
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
ASDAS-CRP	Ankylosing Spondylitis Disease Activity Score-CRP
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index

Acknowledgements

Not applicable.

Authors' contributions

GD: making of the study design, collection of data, interpretation and analysis of the data, writing of the paper, and final approval of the article. MA: collection of data, analysis, and interpretation of data. MSB: collection of data and writing of the paper. The authors have read and approved the final manuscript.

Funding

Recep Tayyip Erdogan University, Scientific Research Projects Coordination Unit supported this study. Project Title: Relationship between Galectin-3 Level and Disease Activity in Patients with Ankylosing Spondylitis (Project n. TSA-2017–713).

Availability of data and materials

All data and materials are showed in the main paper.

Declarations

Ethics approval and consent to participate

This study was conducted by the principles of the Declaration of Helsinki. Ethical approval Recep Tayyip Erdogan University supported this study (Ref. no.: 2016–85/102). An informed and written consent was taken from each participant.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 6 April 2023 Accepted: 5 June 2023
Published online: 22 June 2023

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