ORIGINAL ARTICLE

Serum human cartilage glycoprotein-39 levels in patients with systemic lupus erythematosus

Dominika Wcisło-Dziadecka[1], Anna Kotulska[2], Ligia Brzezińska-Wcisło[1], Eugeniusz J. Kucharz[2], Anna Lis-Święty[1], Grażyna Kamińska-Winciorek[1]

1 Department of Dermatology, Medical University of Silesia, Katowice, Poland
2 Department of Internal Medicine and Rheumatology, Medical University of Silesia, Katowice, Poland

KEY WORDS

human cartilage glycoprotein-39, systemic lupus erythematosus

ABSTRACT

INTRODUCTION Human cartilage glycoprotein-39 (HC gp-39) is a protein secreted by various cells including chondrocytes. Serum HC gp-39 has been suggested to be a marker of cartilage damage. However, inflammation involving other sites than the joints is an additional factor that increases the serum level of HC gp-39.

OBJECTIVES The aim of the study was to evaluate the usefulness of HC gp-39 determination in serum of patients with systemic lupus erythematosus (SLE) as a marker of joint involvement.

PATIENTS AND METHODS Serum HC gp-39 levels were measured in 25 patients with SLE and 22 healthy controls. SLE activity was assessed by the Systemic Lupus Erythematosus Disease Activity Index, and articular involvement by calculating the number of swollen and tender joints. The markers of inflammation (erythrocyte sedimentation rate, C-reactive protein) were determined.

RESULTS We observed an increase in HC gp-39 in SLE patients. However, there was no correlation of this parameter with disease activity, inflammatory markers (except serum γ globulin levels), and articular involvement.

CONCLUSIONS The study suggests that increased HC gp-39 in SLE patients results mainly from inflammation and is not useful as a marker of joint involvement.

INTRODUCTION Human cartilage glycoprotein-39 (HC gp-39), also referred to as YKL-40, is a protein produced by human chondrocytes, synovial cells, macrophages, and neutrophils.[1,2] The physiological role of HC gp-39 remains unknown, although contribution to angiogenesis control and regulation of the connective tissue remodeling have been suggested as its putative functions.[3]

Increased serum levels of HC gp-39 were found in patients with rheumatoid arthritis, and were therefore associated with articular damage and inflammation. Peptides derived from HC gp-39 bind to DR4 molecules on peripheral blood T cells from patients with rheumatoid arthritis. On the basis of this finding, HC gp-39 has been suggested to be involved in the pathogenesis of rheumatoid arthritis.[4,5]

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting various organs. SLE patients suffer from arthralgias or even arthritis that might lead to joint damage. So far, only a few studies have investigated the serum level of HC gp-39 in patients with SLE. Vos et al.[6,7] showed increased serum HC gp-39, but there was no correlation with clinical and laboratory parameters of disease activity or inflammation. The present study was designed to evaluate serum HC gp-39 levels in patients with SLE in relation to their joint manifestations.

PATIENTS AND METHODS Twenty-five women with SLE were examined. A mean age of patients was 44 years, mean period of overt disease prior to the study was 10.5 years. A control group comprised 22 healthy women (mean age, 41 years). The body mass index (BMI) of patients and controls was similar (23.2 ±4.2 and 25.2 ±3.8 kg/m^2, respectively). Diagnosis of SLE was based on the modified American College of Rheumatology

Correspondence to:
Prof. Eugeniusz J. Kucharz, MD, PhD, Katedra i Klinika Chorób Wewnętrznych i Reumatologii, Śląski Uniwersytet Medyczny, ul. Ziołowa 45/47, 40-635 Katowice, Poland, phone: +48-32-359-82-90, fax: +48-32-202-99-33, e-mail: ejkucharz@poczta.onet.pl
Received: August 27, 2009.
Revision accepted: November 9, 2009.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2009; 119 (12): 785-788

TABLE Serum human cartilage glycoprotein-39 level and other laboratory parameters in patients with systemic lupus erythematosus and healthy controls (mean ± standard deviation)

Group	HC gp-39 (ng/ml)	CRP (ng/ml)	ESR		γ globulin protein fraction (%)
			(mm/1 h)	(mm/2 h)	
controls (n = 22)	36.4 ±14.9	2447.6 ±1600.1	7.7 ±3.4	15.8 ±5.1	13.9 ±1.1
SLE (n = 25)	65.2 ±43.0[a]	9884.3 ±1867.7[a]	24.0 ±25.2	43.9 ±36.0	15.8 ±2.9

a statistical significance of the difference $P < 0.005$

Abbreviations: CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, HC gp-39 – human cartilage glycoprotein-39, SLE – systemic lupus erythematosus

classification criteria.[8] Patients with overlapping syndromes or other concomitant disorders were excluded. All the examined patients had active disease (Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] >10), and most of them had organ involvement. There was no patient with renal failure requiring dialysis. All patients were receiving treatment for SLE.[9] Corticosteroids were administered in all patients (mean daily dose equivalent of 22 mg prednisone), some patients received other medications as well (cyclophosphamide, azathioprine, mofetil mycophenolate). Venous blood samples were collected in the morning after overnight fasting.

Serum HC gp-39 was measured with a commercially available enzyme-linked immunosorbent assay, using METRA YKL-40 kit (Quidel Co., San Diego, California, United States). All measurements were done in duplicate. The erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), antinuclear antibody (ANA), and protein fractions were determined using routine methods. To assess disease activity we used the SLEDAI,[10] because it has been shown to be a valid measure in multiple patient groups, and also to be sensitive to signs and symptoms of internal organ involvement.[11] Articular involvement in patients with SLE was evaluated by calculating the number of swollen and tender joints. We also used an index for rheumatoid arthritis activity, the Disease Activity Score (DAS) 28, because it includes the assessment of 28 joints for tenderness and swelling, as well as the ESR. The DAS 28 index was calculated like in rheumatoid arthritis patients (DAS 28 = 0.54 times √ [number of tender joints] + 0.039 times number of swollen joints + 0.72 times natural logarithm ESR + 0.14).[12]

Data distribution was analyzed with the Shapiro-Wilk test. The U Mann-Whitney test was used to compare the groups because the obtained results were not normally distributed. Correlation coefficients were calculated and tested using the Spearman's rank test.

RESULTS Mean serum levels of HC gp-39 were almost twice higher in SLE patients than in controls. The HC gp-39 level was above 51.3 ng/ml (i.e., mean ± standard deviation of the control group) in 14 SLE patients (60%) (TABLE).

There was no correlation between serum HC gp-39 levels and age, BMI, duration of symptoms, serum CRP, ANA titre, or ESR. A positive correlation was found between HC gp-39 and γ globulin in SLE patients ($r = 0.40$, $P < 0.05$). There was no such correlation in controls. There was no association between HC gp-39 levels and disease activity measured with the SLEDAI. There was no difference in serum HC gp-39 between the subgroups of patients with the SLEDAI <30 (10 patients) and those with the SLEDAI >30 (15 patients) or those treated with different doses of glucocorticosteroids.

When SLE patients were classified according to the degree of articular involvement, there was no correlation between serum HC gp-39 levels and the number of swollen, tender joints or DAS 28 (data not shown).

DISCUSSION Articular involvement in SLE is different from that in rheumatoid arthritis. In the latter, inflammation of the synovial membrane results from infiltration with activated lymphocytes and major histocompatibility complex class II expressing cells, and this phenomenon may be related to altered peptide ligand based on the HC gp-39 epitope.[13] In SLE patients, inflammatory arthritis rarely leads to joint destruction and is believed to be an immune-mediated reaction or a result of deposition of immune complexes within the joints.

HC gp-39 was initially thought to be an index of cartilage damage but subsequent studies revealed that it should be considered as an index of chondrocyte activation.[14] This process is related to inflammation and may be associated with cartilage damage because it occurs in rheumatoid patients, while it is not associated with significant joint damage in SLE patients with immune-induced chondrocyte activation.

Our results suggest that HC gp-39 cannot be considered as a marker of articular damage in patients with SLE, which is consistent with the previous findings of Vos et al.[6,7] The mechanism that accounts for secretion of HC gp-39 remains unclear. The open question is what is a role of systemic inflammation in stimulation of HC gp-39 secretion. In the present study, there was no correlation between serum HC gp-39 and CRP. It might suggest that HC gp-39 is released by activated chondrocytes only, but it is not an acute

phase reactant, and the local inflammation within the synovial membrane is the major trigger for HC gp-39 release. The role of immune-mediated activation of chondrocytes in secretion of HC gp-39 is supported by the correlation between serum HC gp-39 and γ globulin levels.

Our results do not suggest that HC gp-39 measurement should be applied for clinical purposes as a marker of articular involvement in patients with SLE; nonetheless, the mechanism of increased HC gp-39 in these patients is a phenomenon that deserves further investigation.

REFERENCES

1 Hakala BE, White C, Recklies AD. Human cartilage gp-39, a major secretory product of articular chondrocytes and synovial cells, is a mammalian member of a chitinase protein family. J Biol Chem. 1993; 268: 25803-25810.

2 Wcisło-Dziadecka D, Kotulska A, Kucharz EJ. [Human cartilage glycoprotein-39: structure, biological function and application in clinical diagnostics]. Reumatologia. 2005; 43: 147-153. Polish.

3 Recklies AD, White C, Ling H. The chitinase 3-like protein human cartilage glycoprotein-39 (HC gp-39) stimulates proliferation of human connective tissue cells and activates both extracellular signal-regulated kinase- and protein kinase B-mediated signaling pathways. Biochem J. 2002; 365: 119-126.

4 Verheijden GF, Rijnders AW, Bos E, et al. Human cartilage glycoprotein-39 as a candidate autoantigen in rheumatoid arthritis. Arthritis Rheum. 1997; 40: 1115-1125.

5 van Bilsen JH, van Dongen H, Lard LR, et al. Functional regulatory immune responses against human cartilage glycoprotein-39 in healthy vs. proinflammatory responses in rheumatoid arthritis. Proc Natl Acad Sci U S A. 2004; 101: 17180-17185.

6 Vos K, Miltenburg AM, van Meijgaarden KE, et al. Cellular immune response to human cartilage glycoprotein-39 (HC gp-39)-derived peptides in rheumatoid arthritis and other inflammatory conditions. Rheumatology. 2000; 39: 1326-1331.

7 Vos K, Steenbakker P, Miltenburg AM, et al. Raised human cartilage glycoprotein-39 plasma levels in patients with rheumatoid arthritis and other inflammatory conditions. Ann Rheum Dis. 2000; 59: 544-548.

8 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997; 40: 1725.

9 Walace DJ. New European recommendations (European League Against Rheumatism 2008) for management of lupus erythematosus: American perspective. Pol Arch Med Wewn. 2008; 118: 402-403.

10 Bombardier C, Gladman D, Urowitz M, et al. Derivation of SLEDAI: a disease activity index for lupus patients. Arthritis Rheum. 1992; 35: 630-640.

11 Olesińska M, Więsik-Szewczyk E, Chwalińska-Sadowska H. [Evaluation of systemic lupus erythematosus activity during pregnancy]. Pol Arch Med Wewn. 2007; 117: 312-316. Polish.

12 van der Heijde D, Østergaard M. Assessment of disease activity and damage in inflammatory arthritis. In: Bijlsma JW, ed. EULAR Compendium on rheumatic diseases. London, United Kingdom: EULAR; 2009: 182-201.

13 Boots AH, Hubers H, Kouwijzer M, et al. Identification of an altered peptide ligand based on the endogenously presented, rheumatoid arthritis--associated, human cartilage glycoprotein-39 (263-275) epitope: an MCH anchor variant peptide for immune modulation. Arthritis Res Ther. 2007; 9: R71.

14 Lis K. [Biochemical markers of osteoarthritis]. Ann Acad Med Siles. 2008; 62: 123-130. Polish.

ARTYKUŁ ORYGINALNY

Stężenie ludzkiej chrząstkowej glikoproteiny 39 w surowicy chorych na toczeń rumieniowaty układowy

Dominika Wcisło-Dziadecka[1], Anna Kotulska[2], Ligia Brzezińska-Wcisło[1], Eugeniusz J. Kucharz[2], Anna Lis-Święty[1], Grażyna Kamińska-Winciorek[1]

1 Katedra i Klinika Dermatologii, Śląski Uniwersytet Medyczny, Katowice
2 Katedra i Klinika Chorób Wewnętrznych i Reumatologii, Śląski Uniwersytet Medyczny, Katowice

SŁOWA KLUCZOWE

ludzka chrząstkowa glikoproteina 39, toczeń rumieniowaty układowy

STRESZCZENIE

WPROWADZENIE Ludzka chrząstkowa glikoproteina 39 (*human cartilage glycoprotein-39* – HC gp-39) jest białkiem wydzielanym przez różne komórki, w tym chondrocyty. Sugerowano, że stężenie HC gp-39 w surowicy jest wskaźnikiem uszkodzenia chrząstek, ale procesy zapalne pozastawowe są dodatkowym czynnikiem zwiększającym stężenie HC gp-39 w surowicy.

CELE Celem pracy jest ocena przydatności oznaczania stężenia HC gp-39 w surowicy chorych na toczeń rumieniowaty układowy (*systemic lupus erythematosus* – SLE) jako wskaźnika uszkodzenia stawów.

PACJENCI I METODY Stężenie HC gp-39 w surowicy oznaczono u 25 chorych na SLE i u 22 osób zdrowych, stanowiących grupę kontrolną. Aktywność choroby określono za pomocą wskaźnika SLEDAI (Systemic Lupus Erythematosus Disease Activity Index). Zajęcie stawów oznaczono liczbą obrzękniętych lub bolesnych stawów. Oznaczono wskaźniki zapalne (odczyn Biernackiego, stężenie białka C-reaktywnego).

WYNIKI Wykazano zwiększenie stężenia HC gp-39 w surowicy chorych na SLE, ale nie stwierdzono korelacji stężenia HC gp-39 z aktywnością choroby, wskaźnikami zapalenia (z wyjątkiem stężenia γ-globulin), jak również ze stopniem zajęcia stawów przez proces chorobowy.

WNIOSKI Wyniki badania sugerują, że zwiększone stężenie HC gp-39 u chorych na SLE jest głównie skutkiem procesu zapalnego i nie wskazują na przydatność oznaczania HC gp-39 jako wskaźnika uszkodzenia stawów.

Adres do korespondencji:
prof. dr hab. med. Eugeniusz J. Kucharz, Katedra i Klinika Chorób Wewnętrznych i Reumatologii, Śląski Uniwersytet Medyczny, ul. Ziołowa 45/47, 40-635 Katowice, tel.: 032-359-82-90, fax: 032-202-99-33, e-mail: ejkucharz@poczta.onet.pl
Praca wpłynęła: 27.08.2009.
Przyjęta do druku: 09.11.2009.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2009; 119 (12): 785-788