



Role of Soluble Vascular Cell Adhesion Molecule-1 in Knee Osteoarthritis among Postmenopausal Women

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Abstract

Objective: Knee osteoarthritis is the most common form of joint disorder and a leading cause of pain and functional disability among elderly female population or in postmenopausal phase of females. Osteoarthritis is now considered as a low grade inflammatory condition. VCAM-1 is an inducible cell surface glycoprotein and mediates heterotypic cellular aggregation. Therefore, the aim of this study is to assess the role of soluble VCAM-1 in knee osteoarthritis among postmenopausal women.

Materials and Methods: The present study includes 100 postmenopausal women of age 50 years or above with clinical symptoms of knee osteoarthritis as cases and 100 normal healthy female age matched individuals as controls. CRP was assayed in serum by using latex-enhanced turbidimetric immunoassay method. Soluble VCAM-1 and estrogen were estimated by ELISA method in all 200 subjects. Statistical analysis was made by student independent sample t-test. Correlation was determined by using spearman's rank correlation coefficient.

Result: The serum level of soluble VCAM-1 was found statistically highly significantly increased ($p < 0.001$) while estrogen was found highly significantly decreased ($p < 0.001$) in postmenopausal women with symptoms of knee osteoarthritis as compared to control healthy subjects. CRP was also found significantly increased in postmenopausal women with symptoms of knee osteoarthritis as compared to control healthy subjects. A correlative study showed significant negative correlation between VCAM-1 and estrogen hormone while positive correlation between VCAM-1 and CRP in postmenopausal women with symptoms of knee osteoarthritis.

Conclusion: The increased levels of soluble VCAM-1 showed an active inflammation or cartilage damage. Thus, it can be used as a biomarker for the assessment of onset of osteoarthritis.

Keywords: VCAM-1, Knee osteoarthritis, Postmenopausal women, Estrogen.

Introduction

Osteoarthritis is the most common joint disorder and one of the leading causes of pain, functional disability and reduced health-related quality of life. It is characterized by slow progressive

degeneration of articular cartilage, subchondral bone sclerosis, synovial inflammation and marked osteophyte formation, with the involvement of whole joint.^[1] Epidemiological observations showed that after the age of 50, osteoarthritis,

particularly of the knee, is more common in women than in men and suggesting that estrogen deficiency may play an important role in the onset or progression of osteoarthritis.^[2-4] Clinically, this condition is characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of local inflammation. For a long time osteoarthritis was considered as non-inflammatory condition, but now it become evident that low grade of inflammation mainly associated with synovitis has been reported in osteoarthritis.^[5-8] Synovitis is commonly seen in early and advanced phase of osteoarthritis and has been associated with knee pain and cartilage degeneration.^[9-12] C-reactive protein (CRP) serving as a marker for systemic inflammation, several studies showing a relationship between serum CRP levels and osteoarthritis of the knee.^[13-15] Although, CRP is not taken as an optimal marker for inflammation in osteoarthritis; other putative markers have been associated with some osteoarthritis phenotypes. These include proinflammatory cytokines, cell adhesion molecules and adiponectin. The inflammatory changes occur in the synovium include synovial hypertrophy and hyperplasia with infiltration of the underlying tissue by various inflammatory cells.^[16-19] Adhesion molecules play an important role during inflammatory process because they enable inflammatory cells to migrate to inflamed compartment. Vascular cell adhesion molecule-1 is an inducible cell surface sialoglycoprotein expressed on chondrocytes and synovial fibroblasts. VCAM-1 mediates the adhesion of lymphocytes, monocytes, eosinophils, and basophils to vascular endothelium and plays a role in the development of inflammation.^[20] Therefore, the aim of this study is to assess the role of soluble VCAM-1 in postmenopausal women to detect early stage of knee osteoarthritis.

Materials and Methods

The present study has been carried out in the Department of Biochemistry and Department of Orthopaedics, G.R Medical College & J.A. Group

of Hospitals, Gwalior. Total 200 human subjects were taken in the study. Out of which 100 postmenopausal women with symptoms of knee osteoarthritis were taken as cases and 100 normal healthy individuals of same age as control.

Inclusion criteria: Postmenopausal women having no menstruation for more than 12 months with complain of knee pain lasting longer than 1 month in addition to atleast 3 of the following 6 criteria according to American College of Rheumatology Criteria for knee osteoarthritis: age>50 years, morning stiffness more than 30 minutes, crepitus, bony enlargement, bony tenderness and absence of palpable warmth.

Exclusion criteria: Patients taking any hormone replacement therapy (HRT), non steroidal anti inflammatory drugs (NSAID), having any metabolic bone disease, rheumatoid arthritis, serious systemic diseases, history of knee trauma or knee injury, cardiac heart diseases, diabetes. Before starting analysis, the written consent was taken from all subjects. The study has been approved by institutional ethical committee and was carried out by keeping all norms in mind. The clinical manifestations of disease, personal history of patients were recorded in study proforma.

7 ml of blood sample was taken from all subjects under all aseptic precautions. Blood sample was collected in plain vial and incubated at 37°C for 30 minutes. After incubation, clot was removed and remaining sample was taken in centrifuge test tube. Samples were centrifuged at 3000rpm for 10 to 20 minutes. Supernatant was collected in clean and dry serum test tube and stored at -20°C for further estimation of C- reactive protein, estrogen hormone and soluble vascular cell adhesion molecule-1(sVCAM-1). CRP was assayed in serum by latex-enhanced turbidimetric immunoassay. The serum level of soluble VCAM-1 level and estrogen hormone were estimated by ELISA technique. The results were expressed as Mean \pm Standard Deviation. The statistical differences between cases and control were determined by student independent t-test. Correlation was determined by using spearman's

rank correlation coefficient. Data analyses were performed with the Statistical Package for the Social Sciences, version 21.0 (SPSS, Chicago, Illinois, USA). The p value less than 0.05 were considered as significant.

Results

Table No 1: showing the status of CRP, estrogen hormone and soluble VCAM-1 level in control and postmenopausal women with symptoms of knee osteoarthritis (cases). The mean level of CRP was found significantly increased ($p < 0.01$) while the serum levels of soluble VCAM-1 was found statistically highly significantly increased ($p < 0.001$) and estrogen hormone was found highly significantly decreased ($p < 0.001$) in postmenopausal women with symptoms of knee osteoarthritis as compared to control. Table No 2: showing the inverse correlation between soluble VCAM-1 and estrogen hormone while positive correlation between soluble VCAM-1 and CRP in postmenopausal women with symptoms of knee osteoarthritis.

Table No 1: Showing the level of sVCAM-1, estrogen and CRP in control and postmenopausal women with clinical symptoms of knee osteoarthritis

Variable	Control (100)	OA Subjects (100)
Estrogen (pg/ml)	36.19± 15.80	27.31±17.29**
CRP(mg/l)	4.6 ± 1.67	6.6± 5.78*
sVCAM-1(ng/ml)	464.31± 28.54	562.87± 63.78**

*Significant at $p < 0.01$, **HighlySignificant at $p < 0.001$

Table No 2: Showing correlation between sVCAM-1 and other investigated parameters in postmenopausal women with symptoms of knee osteoarthritis:

S.No	Parameters	VCAM-1
1.	CRP	0.329*
2.	Estrogen	-0.281*

Results are presented in r value

*Significant at $p < 0.01$

Discussion

Osteoarthritis is now considered as a whole joint disease in which bone, synovia and other joint structures are affected and adhesion molecules in the circulation contribute to the pathogenesis of osteoarthritis through cell-cell or cell-matrix interactions. In our study, the mean level of serum soluble VCAM-1 was found statistically highly significant ($p < 0.001$) in postmenopausal women with symptoms of knee osteoarthritis as compared to control (Table No 1). This is consistent with the study of Hoeven et al who reported the increased level of VCAM-1 in elderly women having knee osteoarthritis than those without knee osteoarthritis.^[21] Other studies also reported the elevated level of soluble VCAM-1 in serum of patients with osteoarthritis.^[22-24] In joints, VCAM-1 is expressed by microvascular endothelial cells, synovial fibroblasts, and chondrocytes.^[25] It is not appreciably expressed on resting vascular endothelium but is rapidly induced in response to a number of inflammatory stimuli, such as TNF- α , IL-1 β .^[26] During cartilage damage, chondrocytes can produce or respond to a large number of cytokines such as tumor necrosis factor- α and interleukin-1 β .^[27] These proinflammatory cytokine activation alters the phenotype of quiescent endothelial cells, which in turn increases the synthesis of VCAM-1.^[28] The increased level of soluble VCAM-1 in our study shows active cartilage damage or an inflammatory component in osteoarthritis. The cartilage is the prime site of osteoarthritis disease and is very sensitive to change in sex hormone level. Our study showed significant decreased levels of estrogen hormone ($p < 0.001$) in postmenopausal female subjects with symptoms of knee osteoarthritis as compared to control postmenopausal women. This is in agreement with the studies of Sheikh et al^[29]. The correlative study between VCAM-1 and estrogen hormone showed an inverse relationship between them. It may be due to depletion of estrogen hormone during menopause, which induces VCAM-1 production. The mechanism through which estrogen decreases cytokine induced

VCAM-1 production by inhibition of NF- κ B, AP-1 and GATA transcription factors.^[30] In this study the serum level of CRP was also found significantly high in postmenopausal women with symptoms of knee osteoarthritis as compared to control which is in consistent with the study of Spector et al who reported modestly but significant increase of CRP level in women with early stage of knee osteoarthritis^[14]. CRP is an acute phase protein, which reflects a measure of the acute-phase response. Elevated level of CRP in serum may reflect subclinical inflammation in affected joints, mediated by cytokines. Furthermore we also found a positive correlation between CRP and VCAM-1 in this study. Thus, these findings support that inflammation is a component of the early events leading to clinical osteoarthritis.

Conclusion

It is therefore concluded from the study that in postmenopausal women lack of estrogen hormone induces soluble VCAM-1 production. VCAM-1 mediates the interaction of chondrocytes with immune cells and could thus by itself contribute to immune-mediated cartilage damage. Hence, serum level of soluble VCAM-1 could be used as an early biomarker for inflammatory response and cartilage damage in osteoarthritis. If in postmenopausal women the periodic check up for estrogen and VCAM-1 is carried out the occurrence and severity of osteoarthritis could be prevented.

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