Available online at **www.ijmrhs.com**

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2018, 7(5): 18-22

Estimation of Serum Matrix Metalloproteinases-1 Levels in Iraqi Female Patients with Osteoarthritis

Vean Sabah Ali, Zainab A. Aldaher , Sahar H. Abdul-Kareem*, Heba F. Hassan, Rasha M. Shaker and Rasha A. Azeez

Department of Basic Science, College of Dentistry, University of Baghdad, Baghdad, Iraq

**Corresponding e-mail: sahiarhashim1@yahoo.com*

ABSTRACT

This study was established to investigate the correlation between the expression of matrix metalloproteinases (MMP-1) and the pathogenesis of osteoarthritis (OA). Blood samples were collected from 55 female patients with inflammatory OA and controls for estimation of serum (MMP-1) levels. In the current study, there is significant increase ($p<0.001$) in the mean of serum MMP-1 levels in osteoarthritis females (4027.73 ± 1345.28 pg/ml) than that in control females (798.76 ± 136.79 pg/ml). It was concluded that MMP-1 may be associated with the pathogenesis of osteoarthritis.

Keywords: Osteoarthritis, Matrix metalloproteinases, Matrix metalloproteinases-1, Calcium, Alkaline phosphatase, Phosphorus

Abbreviations: ALP: Alkaline Phosphatase; OA: Osteoarthritis; CPC: o-Cresolphthalein Complexone; MMP: Matrix Metalloproteinases; RA: Rheumatoid Arthritis; SF: Synovial Fluid

INTRODUCTION

Osteoarthritis (OA), the most common form of chronic joint disorders, is a process of deterioration and continuous biological breakdown of articular cartilage in synovial joint tissues, including periarticular muscles, subchondral bone, peripheral nerves, synovium, ligaments, and joint capsular tissues [1,2]. OA may occur in any joint, but it is most commonly seen in the hands, feet, hips and facet joints. OA can cause pain, stiffness, swelling, muscle weakness, along with joint instability, all of which may lead to a gradual loss of physical function and poor quality of life [3]. In women between the ages of 55 to 64 years, the prevalence of radiographic OA in the knee is 7.5%, in women older than 65 years, their prevalence increases significantly to 20.3% [4].

Generally, OA has become a leading health issue in the aging population, with approximately 10-20% of all people over 60 years age suffering from symptomatic OA and with more women affected than men after 50 years age [5,6]. The most common risk factors for OA are gender, aging, obesity, genetic predisposition, previous joint injury, and mechanical factors, such as abnormal joint form [7].

Currently, therapeutic treatments that effectively prevent OA therapy exist, and the clinical management of OA mainly involves the control of inflammation, pain, and procedures to improve joint function [8]. Matrix metalloproteinases (MMPs), especially MMP-1, MMP-2, and MMP-9, have emerged as the major candidates for participation in the disease progression of OA [9]. The family of MMP composed of at least 28 members, and all amino acid sequences of MMPs have two conserved domains, prodomain and catalytic domain, which is important to the specificity of their substrate. All the members of the MMP family have broad substrate characteristics, but their main substrates include metalloelastase, collagenases, matrilysins, gelatinases, stromelysins and membrane-type MMPs [10].

Generally, MMPs can decompose any extracellular matrix element, including proteoglycans, laminin, vitronectin, collagens and fibronectin. From development and disease perspective, MMPs are crucial during embryonic development and reproduction, and it plays a major role in tumor growth and metastasis [11]. The main members of the MMP family are MMP-1, MMP-2, and MMP-9. MMP-1 is collagenase and it plays a crucial role in metastasis and tumor progression [12]. MMP-1(collagenase-1), which is primarily created by synoviocytes [13], has been present in an increased concentration in synovial luid of patients suffering from osteoarthritis and joint injuries [14]. MMP-1

is the primary neutral proteinase able to break down native fibrillar collagens of types I, II, III, and V, and it appears to play an important role in the reassembling of collagen connective tissue in various physiological and pathological conditions [15].

MMP-1is an interstitial collagenase that can break down interstitial collagens (types I, II and III) and it is believed that it is the multi-functional molecule with important roles in physiologic processes maintaining osteochondral integrity [16]. A diversity of studies has examined the correlation of the expression of MMP-1, MMP-2, and MMP-9 proteins and the pathogenesis of OA [17,18].

Protein expression levels of MMP-1, MMP-2, and MMP-9 were either reported to be associated with OA or not at all related to OA [19,20]. Therefore, we performed meta-analysis to study the relationship between MMP-1, MMP-2, and MMP-9 expression and the pathogenesis of OA.

MATERIALS AND METHODS

Patients and Control Groups

Thirty Iraqi female patients are chosen from the outpatient clinic in the Department of Rheumatology, Baghdad Teaching Hospital, Medical City, Baghdad, Iraq with inflammatory OA diagnosed according to the recommendations of American College of Rheumatology [21]. All patients were assessed by Kellgren and Lawrence grading criteria for radiographic severity of knee osteoarthritis with different signs and symptoms such as stiffness, joint pain, bony tenderness, bony enlargement, and crepitus [22] with their age ranged 30-45 years (38.47 ± 5.73). The control group consisted of 25 healthy females, matched according to age and gender of patients the mean of age (39.84 ± 4.63) with no complaints of knee pain. Height and weight were measured and body mass index (BMI=kg/m^2) was counted for two groups. During selection of patients, certain exception criteria were followed to exclude unsuitable patients including (ischemic heart diseases, damage or active peptic ulcer, hypertension, history of bladder cancer, hepatic or renal impairment, and lactating female patients and pregnant).

Calcium Concentration

The calcium concentration in both patients and control sample were measured by commercially available kits from (Calcium Liquicolor Photometric Test, CPC Method) with normal values of serum calcium 2.02-2.60 mmol/l.

ALP

The evaluations of ALP in serum were also measured with a commercial reagent kit Alkaline Phosphatase Liquicolor (DEA buffer, DGKC, Orthophosphoric monoester phosphohydrolase, alkaline optimum, EC 3.1.3.1). The normal value of ALP in a woman was considered as 49-232 U/I.

Phosphorus

The kit was used for detection serum phosphorus levels in patient and control group (Phosphorus Liquirapid, Photometric UV Test for determination of phosphorus). The normal value of phosphorus was considered as 0.81-1.62 mmol/l in the adult.

Estimation of Serum MMP-1 Levels

Serum levels of MMP-1 concentrations have been measured by using commercially available ELISA and performed as recommended in the lealet with the kit (Mybiosource-MBS355314, USA).

Statistical Analysis

By using Statistical Package for Social Science (SPSS version 20, IBM, Armonk, USA). In this study, the t-test was used for study data. The results were expressed as a mean ± standard error of mean SEM, the differences in means of the variables between control and patient groups. Correlations between all the studied variables were evaluated using Pearson's correlation coefficient(r) and linear regression analyses were used for the evaluation of data. $P<0.05$ was considered to be statistically significant.

RESULTS

Table 1 showed that the mean age of osteoarthritis patients was 38.47 ± 5.73 years, whereas for healthy subjects

was 39.84 ± 4.63 years with no significant difference (p>0.05). No statistically significant difference (p>0.05) in the mean of BMI among study groups and osteoarthritis group was seen. The mean of BMI was 26.83 ± 3.5 Kg/m^2 and in control group, the mean of BMI was 25.52 ± 4.37 Kg/m^2, as clearly shown in Table 1. The current results showed that there are no significant differences in the mean serum levels of ALP in osteoarthritis patients (64 ± 12.12 U/I) and for control subjects (65.52 ± 15.58 U/I) (p>0.05). Regarding the mean of serum calcium, the current study found that there are no significant differences (p>0.05) in the mean of serum calcium levels among study groups; in osteoarthritis patients, the mean was 2.18 ± 0.22 mmol/l and in healthy females, the mean was 2.252 ± 0.18 mmol/l.

Table 1 Distribution of Ages, BMI, ALP, Ca in the study group

Characteristics		Healthy control (n=25)	Osteoarthritis (n=30)	P-value
Age (years)	Range	15	15	p>0.05
	Mean ± SD	39.84 ± 4.63	38.47 ± 5.73	
	Median	41	39.5	
BMI (Kg/m^2)	Range	16	19	p>0.05
	Mean ± SD	25.52 ± 4.37	26.83 ± 3.5	
	Median	25	27	
ALP	Range	51	49	p>0.05
	Mean ± SD	65.52 ± 15.58	64 ± 12.12	
	Median	60	61.5	
Ca	Range	0.6	0.9	p>0.05
	Mean ± SD	2.252 ± 0.18	2.18 ± 0.22	
	Median	2.2	2.25	

This study noticed that there was a significant increase (p<0.001) in the mean of serum MMP-1levels in osteoarthritis females (4027.73 ± 1345.28 pg/ml) than that in control females (798.76 ± 136.79 pg/ml). Moreover, the present results found that significant elevation in the mean (p<0.05) of serum pH levels in osteoarthritis patients (1.23 ± 0.18 mmol/l) when compared to the healthy females (1.1 ± 0.27 mmol/l) as illustrated in Table 2.

Table 2 The differences in mean serum levels of MMP-1, PH among study groups

Variables		Control group (n=25)	Osteoarthritis (n=30)	p-value
Serum MMP-1	Range	459	4967	P>0.001
	Median	822	3887	
	Mean ± SD	798.76 ± 136.79	4027.73 ± 1345.28	
PH	Range	1	0.8	P>0.05
	Mean ± SD	1.1 ± 0.27	1.23 ± 0.18	
	Median	1.1	1.3	

DISCUSSION

Osteoarthritis (OA) is a degenerative joint disease and it is one of the main causes of disability in developed countries. Osteoarthritis is described by degeneration of articulate cartilage accompanied by sclerosis of the subchondral bones, osteophytes, and joint space narrowing [23]. The present study is consistent with the study conducted by Ziad, et al., stating that there are no statistically significant differences in mean age and BMI among Iraqi osteoarthritis patients which contain 78% females and 72% healthy females [24]. Yazmalar, et al., found that serum calcium levels did not differ significantly between 74 patients with knee osteoarthritis and 70 controls [25]. Another study supported the result that was previously reported by Zolli, et al. [26]. No statistically significant difference in calcium serum levels was found among osteoarthritis patients and controls. It is known that matrix metalloproteinases (MMPs) appear in OA cartilage and are thought to be involved in the deterioration of cartilage extracellular matrix (ECM) [27]. Participation of ROS in age-related MMP expression provides a mechanistic link between the theory of free radicals of aging and many age-related degenerative diseases such as OA [28]. MMP-1, which belongs to the collagenase subgroup within the MMP family, can degrade the triple helical chains of the type-II collagen of articular cartilage and can exert significant influence on abnormal collagen circulation in OA [13]. The collagen network of articular cartilage consists mainly of type-II collagen, which provides the articular cartilage with elasticity and deformity [29]. Collagen network degradation greatly reduces tissue elasticity and deformation, which is considered one of the oldest modifications in cartilage degeneration [30]. This result agrees with numerous studies indicated that the correlation with MMP1 and

OA. Zeng, et al., pointed out to that the patients with knee OA have significantly higher serum MMP-1 concentrations as compared to serum MMP-1 concentrations in healthy control group [31]. Also, another study showed that in 98 patients with early untreated RA of less than 12 months duration serum MMP-1 levels were significantly greater in RA patients than in controls and serum MMP-1 levels correlate with disease activity and prediction of functional outcome and radiography in early untreated RA [32]. Also, Tchetverikov et al., who found that the highest level of MMP in the SF of patients with RA for proMMP-1, -3, -8, and -9. While MMP-3 and -9 were also detected in control SF, MMP-1 and -8 were found in SF control only at very low concentrations [33]. Yashihara, et al. showed that the levels of MMP-1 and MMP-3 were interrelated with each other in RA and OA groups, may indicate the source of predominant cell of these MMPs: macrophages and neutrophils for MMP-8 and -9 and synovial cells for MMP-1 and -3 [34]. Therefore, the increased protein levels of MMP-1in individuals with OA compared to normal people, which were shown in this meta-analysis, have significant biological consequences on disease progression and significant implications for early diagnosis and treatment of OA [31]. There were some limitations in the current meta-analysis. First, the sample sizes in the studies were relatively small. Second, the absence of some data in studies published in the world [31]. It can be summarized that the protein levels of MMP-1, may be associated with the pathogenesis of OA and that there were differences in the expression of these proteins in the serum.

DECLARATIONS

Conflict of Interest

The authors have disclosed no potential conflicts of interest, financial or otherwise.

REFERENCES

[1] Dreier, Rita. "Hypertrophic differentiation of chondrocytes in osteoarthritis: the developmental aspect of degenerative joint disorders." *Arthritis Research & Therapy,* Vol. 12, No. 5, 2010, p. 216.

[2] Lane, N.E., et al. "OARSI-FDA initiative: defining the disease state of osteoarthritis." *Osteoarthritis and Cartilage,* Vol. 19, No. 5, 2011, pp. 478-82.

[3] Bennell, Kim L., and Rana S. Hinman. "A review of the clinical evidence for exercise in osteoarthritis of the hip and knee." *Journal of Science and Medicine in Sport,* Vol. 14, No. 1, 2011, pp. 4-9.

[4] Felson, David T. "Epidemiology of hip and knee osteoarthritis." *Epidemiologic Reviews,* Vol. 10, 1988, pp. 1-28.

[5] Bijlsma, Johannes WJ, Francis Berenbaum, and Floris PJG Lafeber. "Osteoarthritis: an update with relevance for clinical practice." *The Lancet,* Vol. 377, No. 9783, 2011, pp. 2115-26.

[6] Ekman, Evan F., et al. "Efficacy and safety of intravenous tanezumab for the symptomatic treatment of osteoarthritis: 2 randomized controlled trials versus naproxen." *The Journal of Rheumatology,* 2014, jrheum-131294.

[7] Blagojevic, M., et al. "Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis." *Osteoarthritis and Cartilage,* Vol. 18, No. 1, 2010, pp. 24-33.

[8] Xu, Lin, et al. "Attenuation of osteoarthritis progression by reduction of discoidin domain receptor 2 in mice." *Arthritis & Rheumatology,* Vol. 62, No. 9, 2010, pp. 2736-44.

[9] Murphy, Gillian, and Hideaki Nagase. "Reappraising metalloproteinases in rheumatoid arthritis and osteoarthritis: destruction or repair?" *Nature Reviews Rheumatology,* Vol. 4, No. 3, 2008, p. 128.

[10] Hemmann, Stefanie, et al. "Expression of MMPs and TIMPs in liver fibrosis–a systematic review with special emphasis on anti-fibrotic strategies." *Journal of Hepatology,* Vol. 46, No. 5, 2007, pp. 955-75.

[11] Łukaszewicz-Zając, Marta, et al. "Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) in the tumors of central nervous system (CNS)." *Journal of Neural Transmission,* Vol. 121, No. 5, 2014, pp. 469-77.

[12] Lepetsos, Panagiotis, et al. "Association of MMP-1-1607 1G/2G (rs1799750) polymorphism with primary knee osteoarthritis in the Greek population." *Journal of Orthopaedic Research* 32.9 (2014): 1155-1160.

[13] Wassilew, Georgi I., et al. "The expression of proinflammatory cytokines and matrix metalloproteinases in the synovial membranes of patients with osteoarthritis compared with traumatic knee disorders." *Arthroscopy,* Vol. 26, No. 8, 2010, pp. 1096-1104.

[14] Tchetverikov, I., et al. "MMP protein and activity levels in synovial fluid from patients with joint injury, inflammatory arthritis, and osteoarthritis." *Annals of the Rheumatic Diseases,* Vol. 64, No. 5, 2005, pp. 694-98.

[15] Birkedal-Hansen, H.W.G.I., et al. "Matrix metalloproteinases: a review." *Critical Reviews in Oral Biology & Medicine,* Vol. 4, No. 2, 1993, pp. 197-250.

[16] Rübenhagen, René, et al. "Interleukin-7 levels in synovial fluid increase with age and MMP-1 levels decrease with progression of osteoarthritis." *Acta Orthopaedica,* Vol. 83, No. 1, 2012, pp. 59-64.

[17] Jackson, Miriam T., et al. "Activation of matrix metalloproteinases 2, 9, and 13 by activated protein C in human osteoarthritic cartilage chondrocytes." *Arthritis &Rheumatology,* Vol. 66, No. 6, 2014, pp. 1525-36.

[18] Tío, Laura, et al. "Characterization of opticin digestion by proteases involved in osteoarthritis development." *Joint Bone Spine,* Vol. 81, No. 2, 2014, pp. 137-41.

[19] Heard, Bryan J., et al. "Matrix metalloproteinase protein expression profiles cannot distinguish between normal and early osteoarthritic synovial fluid." *BMC Musculoskeletal Disorders,* Vol. 13, No. 1, 2012, p. 126.

[20] Xue, Meilang, et al. "Endogenous MMP-9 and not MMP-2 promotes rheumatoid synovial fibroblast survival, inflammation and cartilage degradation." *Rheumatology,* Vol. 53, No. 12, 2014, pp. 2270-79.

[21] Gamble, Roche, et al. "Recommendations for the medical management of osteoarthritis of the hip and knee." *Arthritis & Rheumatology,* Vol. 43, No. 9, 2000, pp. 1905-15.

[22] Kellgren, J.H., and J.S. Lawrence. "Radiological assessment of osteoarthrosis." *Annals of the Rheumatic Diseases,* Vol. 16, No. 4, 1957, p. 494.

[23] Creaer, P., and Me Hochbcrg. "Osteoarthritis." *Lancet,* Vol. 350, 1997, pp. 503-508.

[24] Ziad S. Alorawi., Faiq I. Gorial and wafi H. Ali. "Fibromyalgia Syndrome among Iraqi Patients with Knee osteoarthritis." *Journal of the Faculty of Medicine, Baghdad*, Vol. 56, No. 1, 2014,

[25] Yazmalar, L., et al. "Seasonal disease activity and serum vitamin D levels in rheumatoid arthritis, ankylosing spondylitis and osteoarthritis." *African Health Sciences,* Vol. 13, No. 1, 2013, pp. 47-55.

[26] Zoli, Angelo, et al. "Osteoporosis and bone metabolism in postmenopausal women with osteoarthritis of the hand." *Menopause,* Vol. 13, No. 3, 2006, pp. 462-66.

[27] Imai, Kazushi, et al. "Expression of membrane-type 1 matrix metalloproteinase and activation of progelatinase A in human osteoarthritic cartilage." *The American Journal of Pathology,* Vol. 151, No. 1, 1997, p. 245.

[28] Dasgupta, Jaya, et al. "Reactive oxygen species control senescence-associated matrix metalloproteinase-1 through c-Jun-N-terminal kinase." *Journal of Cellular Physiology,* Vol. 225, No. 1, 2010, pp. 52-62.

[29] Wu, Hongbin, Jingyuan Du, and Qixin Zheng. "Expression of MMP-1 in cartilage and synovium of experimentally induced rabbit ACLT traumatic osteoarthritis: immunohistochemical study." *Rheumatology International,* Vol. 29, No. 1, 2008, p. 31.

[30] Dejica, Valeria M., et al. "Increased type II collagen cleavage by cathepsin K and collagenase activities with aging and osteoarthritis in human articular cartilage." *Arthritis Research & Therapy,* Vol. 14, No. 3, 2012, p. R113.

[31] Zeng, G.Q., et al. "High MMP-1, MMP-2, and MMP-9 protein levels in osteoarthritis." *Genetics and Molecular Research,* Vol. 14, No. 4, 2015, pp. 14811-22.

[32] Green, M.J., et al. "Serum MMP-3 and MMP-1 and progression of joint damage in early rheumatoid arthritis." *Rheumatology,* Vol. 42, No. 1, 2003, pp. 83-88.

[33] Tchetverikov, I., et al. "MMP profile in paired serum and synovial fluid samples of patients with rheumatoid arthritis." *Annals of the Rheumatic Diseases,* Vol. 63, No. 7, 2004, pp. 881-83.

[34] Yoshihara, Yasuo, et al. "Matrix metalloproteinases and tissue inhibitors of metalloproteinases in synovial fluids from patients with rheumatoid arthritis or osteoarthritis." *Annals of the Rheumatic Diseases,* Vol. 59, No. 6, 2000, pp. 455-61.