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Study of serum matrix metalloproteinase-1 [MMP-1] in Knee osteoarthritic postmenopausal women

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ABSTRACT:

Objective
To determine the association of serum MMP-1 between postmenopausal females with knee osteoarthritis (Case) and postmenopausal females without knee osteoarthritis (Control).

Design
Case-control study

Method
The study involved 200 female subjects between the ages of 45-70 years. Out of these, 100 were healthy female postmenopausal controls, while the other 100 were postmenopausal female patients suffering from knee osteoarthritis. The study protocol was approved by the Institutional Ethical Committee of UPUMS, Saifai, Etawah. Serum MMP-1 levels were measured in all samples using an ELISA analyzer, following the manufacturer's instructions on a commercial kit. The results are expressed as arithmetic means with standard deviation, and a p-value of less than 0.05 is considered statistically significant. Paired sample t-test was used to analyze the data.

Results
It was observed that the level of Serum MMP-1 was significantly higher (p=0.0001) in cases (533.92±178.51) as compared to controls (42.76±29.19). This finding suggests that MMP-1 levels can be considered a reliable biochemical marker for the diagnosis of osteoarthritis (OA).

Conclusion
Postmenopausal women with knee OA show a significant association with serum MMP-1, making it a useful diagnostic marker.

Key Words: Collagenases, Matrix Metalloproteinase 1, Osteoarthritis

INTRODUCTION-

Osteoarthritis (OA) is a common joint disorder that causes pain, loss of function, and disability

in adults (1). OA can affect any synovial joint in the human body, especially the fingers, knees, and hips. The knee is one of the most commonly affected areas, and old age is the most common cause of OA knee. Most people will eventually develop some degree of osteoarthritis due to factors such as age, lifestyle, metabolic changes, genes, biomechanical forces, or injuries. People with certain occupations that include a lot of strenuous activity are more prone to develop knee osteoarthritis due to continuous pressure on the knee joint (2). Women aged 45 and older are more likely than men to develop osteoarthritis of the knee (3). Biomechanical signaling may initiate the pathology of OA, and signaling through integrin adhesion molecules has been associated with cartilage damage (4, 5). Chondrocytes also produce proinflammatory cytokines, creating their inflammatory environment and increasing the synthesis of matrix-degrading proteinases (6, 7). The cartilage breakdown products are released into the joint fluid and synovitis of the joint space occurs, this inflammation stimulates the release of inflammatory mediators from synovial tissue and initiates the recruitment of new mononuclear inflammatory cells to joint tissues (7, 8). Eventually, a feedforward loop is created as fragments of cartilage broken down by proteinases produced by the chondrocytes irritate the synovium (9).

Inflammatory cytokines stimulate the production of matrix metalloproteinases (MMPs), enzymes that can degrade all components of the extracellular matrix. MMP-1 is the most abundantly expressed collagenase in cartilage and synovium. It is the primary neutral proteinase that can break down native fibrillary collagens of types 1, 2, 3, and 5 and play a significant role in the reassembling of collagen connective tissue in various conditions. It is probably the major mediator of collagen degradation and irreversible joint destruction (4).

In this study, we will be studying the serum MMP-1 levels in knee osteoarthritic postmenopausal females and comparing them with postmenopausal females without osteoarthritis. If we obtain positive results, the diagnostic routine of osteoarthritic patients could be changed significantly, allowing earlier diagnosis and potentially saving the patient's joint and mobility, thereby improving their quality of life.

MATERIALS AND METHODS

The following study was conducted on a sample of 200 female subjects aged between 45-75 years. These subjects were patients of the Orthopedic Out-Patient Department [OPD] of the U.P University of Medical Sciences, Saifai, Etawah. Among these 200 subjects, 100 were postmenopausal females who did not have osteoarthritis (controls), and the other 100 were postmenopausal females who were diagnosed with knee osteoarthritis (cases) using the Kellgren and Lawrence system for radiographic classification of knee OA (10). The orthopedician present in the OPD diagnosed the cases. The control group was also selected from the orthopedics OPD. OA diagnosed cases were considered only after a minimum of 2-3 years of onset of symptoms.

About 2 ml of venous blood was collected from all subjects and informed verbal and written consent was obtained from each of them. The blood samples were centrifuged at 5000 rpm for 5 minutes, and the serum was collected and stored at -20^0C until analyzed. Serum MMP-1 was measured simultaneously in all samples by double antibody sandwich ELISA following the manufacturer's instructions on a commercial kit [Qayee-Bio; Cat. No.: QY-E03001]. Statistical analysis was performed using statistical software carried out on Statistical Package for the Social Sciences [SPSS] 24.0 version. The data is expressed as arithmetic means with standard deviation, with $P<0.05$ considered statistically significant. The biochemical parameter level was evaluated by dependent paired sample t-test.

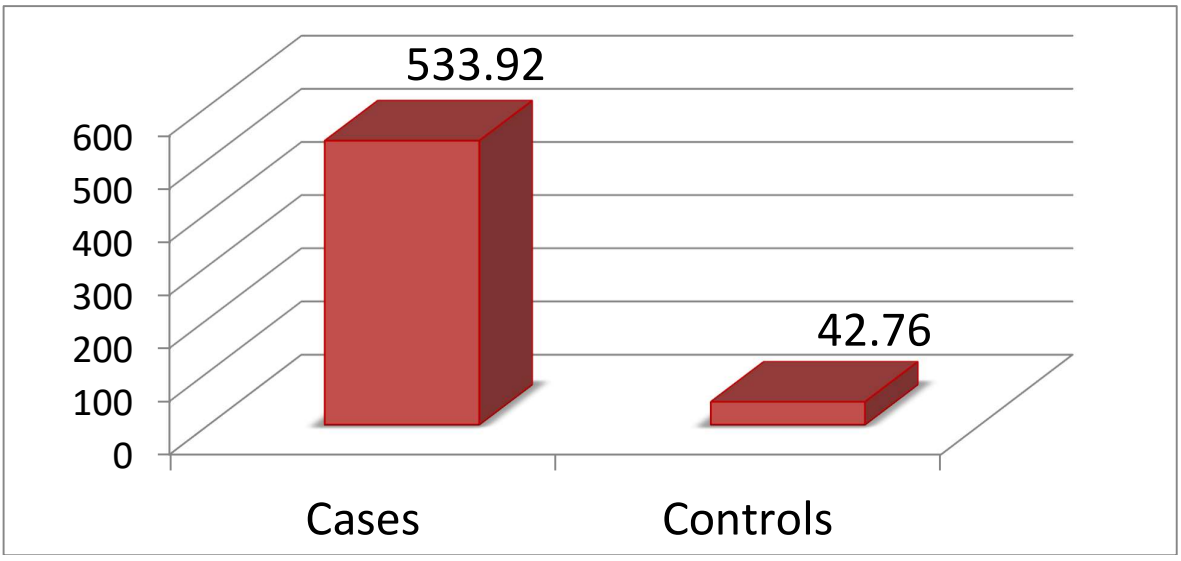
The study was conducted from January 2017 to June 2018. During the selection of patients, certain exclusion criteria were followed to exclude unsuitable patients, including those with osteoarthritis and other arthropathies, those who had undergone surgical removal of ovaries, uterus, or both, those who used Hormonal therapy, chemotherapy/radiotherapy, those with malignancy like uterine cancer, Endometriosis, and Collagen Diseases.

TABLE 1: Status of serum MMP-1 in cases (postmenopausal females with knee osteoarthritis) and controls (postmenopausal females without knee osteoarthritis).

STUDY GROUPS	STUDY PARAMETERS	SERUM MMP-1(pg/ml)
Postmenopausal females without knee osteoarthritis [n = 100]	MIN.	12.31
	MAX.	121.878
	MEAN ± SD	42.76 ± 29.19
	SE	2.91
Postmenopausal females with knee osteoarthritis [n = 100]	MIN.	121.63
	MAX.	998.2
	MEAN ± SD	533.92 ± 178.51
	SE	17.85
p-value* (of cases and controls)		0.0001

*Chi-square test

FIGURE 1: Status of the mean of serum MMP-1 in cases (postmenopausal females with knee osteoarthritis) and controls (postmenopausal females without knee osteoarthritis).



RESULT

The findings of the study were presented in frequencies, percentages, and mean with standard deviation (SD). It was observed that serum MMP-1 levels were significantly higher among cases (533.92±178.51) than controls (42.76±29.19). Furthermore, the serum MMP-1 levels were significantly increased (p value<0.0001) among postmenopausal females without knee osteoarthritis when compared to female controls without knee osteoarthritis.

DISCUSSION-

Osteoarthritis is a chronic disease that affects all joints, particularly the knees. It leads to irreversible damage and affects the joint as a whole. Inflammatory cytokines stimulate the formation of matrix metalloproteinases (MMPs), which are enzymes that can destroy all components of the extracellular matrix.

Despite the small number of patients the results reached significance. It is important to note that our observations derived from female patients, reflecting an epidemiological proportion of OA in the region.

Serum MMP-1, the enzyme biochemical marker in our study was found to be significantly (p=0.0001) higher among cases (533.92±178.51) compared to controls (42.76±29.19).This is consistent with the studies of Ali et al., who indicated that MMP-1 may be associated with the pathogenesis of OA (11). Also Tchetverikov et al., who found that the highest level of MMP in synovial fluid (SF) of patients with Rheumatoid arthritis 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 at low concentrations (12). Zeng et al., pointed out that patients with knee OA have significantly raised serum MMP-1 concentrations as compared to serum MMP-1 concentrations in healthy control group. (13). Again supported by A.Kaspiris et al., it was concluded that MMP-1 expression by osteoblasts, the lining cells of the subchondral bone and subchondral cysts in advanced OA stages, may contribute to the pathological tissue remodeling and the osteochondral changes in OA (14). Our data are in agreement with the study of Sasaki et al., showing that stromal lining cells and osteoblasts would express MMP-1, upon mechanical stimulation, thus preparing recruitment sites for osteoclasts (15). Furthermore Yoshihara et al., stated 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 MMP-9 and synovial cells for MMP-1 and -3 (16).

MMP is an upcoming marker which is also studied and supported by Osteoarthritis Research Society International [OARSI]. It is the only organization dedicated exclusively to advancing OA research.

This study has strengths and limitations. The study time frame may not fully capture the arthritis development processes. It also has some genetic differences, geographical position differences.

As far as Generalizability is concerned, this study can't be generalized, as urban population is not included which can differ in socio economic status, BMI status etc.

Also, number of cases were also less to conclude to a decision.

To the best of our knowledge, this kind of study has been studied by scientists native to China, Iraq, Florida, and Ireland so the novelty of this study is in the geographical area of our interest i.e. rural area of India (Saifai, Etawah, UP.)

In summary, we can undoubtedly state that MMP-1 is representing a new and promising future for Osteoarthritis diagnosis.

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