

Determination Of Clinical Utility Of Novel Biochemical Markers In Osteoarthritis

ABSTRACT

INTRODUCTION

Osteoarthritis is a progressive joint disease characterized by loss of articular cartilage, joint bone hypertrophy, subchondral sclerosis, and chemical and morphological alterations in the synovial membrane and joint capsule. Stiffness, soreness, and focused dislocation of the articular cartilage are changes in the disease seen at the last level of OA, as well as synovial inflammation. Pain is a common clinical symptom, especially after prolonged exercise and weight bearing, and stiffness occurs after inactivity. Biologic markers will also play an important role in the production and monitoring of new structure-modifying therapies for osteoarthritis due to their rapid changes in response to treatment.

AIM: We conducted an observational study to estimate biochemical markers in the knee osteoarthritis patients who came to SMHRC Nagpur for a routine visit.

MATERIAL AND METHODS:

The study included 60 people who visited Shalinitai Meghe hospital in Nagpur for a health check-up. We were able to keep the two groups apart here. The control group is comprises of Healthy Volunteer, while the study group is made up Knee osteoarthritis patients. Each community consists of 30 patients. COMP, Endoglin, Osteopontin, Hs-CRP: all of these parameters were estimated by commercially available ELISA kit.

RESULTS:

The levels of COMP, Endoglin, Osteopontin, and Hs-CRP in the study group were significantly higher than in the control group. In synovial fluid detection, endoglin levels in the sample group are not significantly higher than in the control group. Endoglin levels in the blood increase, as do other parameters.

CONCLUSION:

These findings show a significant increase in the systematic and local development of these biomarkers in the main OA of the knee, as well as the link between disease severity and its production, meaning that they may be involved in OA pathogenesis. Longitudinal studies with repetitive measurements of these biomarkers in plasma and synovial fluid and their interactions with knee pain OA are necessary to track or predict the clinical course of OA and, ultimately, determine their potential role in determining the best time to participate.

KEYWORDS: Osteoarthritis, COMP, Synovial Fluid, Subchondral sclerosis and Endoglin

INTRODUCTION

Rheumatoid arthritis is found in two Greek words: **arth**, meaning joint, and **itis**, meaning **inflammation**. There are more than 100 different types of arthritis (Osteoarthritis, Rheumatoid arthritis, Ankylosing spondylitis, Gout, **Tuberculosis arthritis**). **Osteoarthritis is the most common form of arthritis worldwide.**^{1,2} **Osteoarthritis (OA) is a very common condition, and its spread is expected to increase as more** people reach the age of 60.³

Osteoarthritis (OA) is the most common form of arthritis, affecting an estimated 27 million people in the United States.^{4,5} **Country, or approximately 12% of adults.** By 2030, that figure is expected to reach 72 million, or about 20 percent of the adult population in the United States. Revenues due to OA are estimated to exceed \$ 100 billion.⁶ In India, OA is the most common communicable disease, present in 22 to 39 percent.^{7,8} This is the most common cause of locomotor malfunction, as well as difficult financial and health resources.⁹

After 50 years, 1 person in 5 develops OA. It affects women twice as often as men and often damages knee joints. Those who have previously had a knee injury, are overweight, or have improper alignment of the bones (e.g. bow legs) may be affected.¹⁰

New tissue-specific markers, such as COMP, osteopontin, endoglin, and hs-CRP, have been developed in recent years. **The rise or fall of some of these marks has been linked to the rapid development of joint demolition in patients with OA of the knee in future studies.** Since the difference between degeneration and retaliation processes is thought to be a major factor in the development of cohesive integration, the combination of markers representing these two processes seems promising.

COMP, also known as thrombospondin⁵, is a non-collagenous glycoprotein with 524 kDa MW. It is a thrombospondin protein family that binds to extracellular calcium, which often participates in the cellular matrix assembly and matrix-matrix protein interaction. COMP is made up of five identical units.¹¹ The arrangement of collagen fibers is facilitated by COMP. The exact function of COMP is unclear, but by its interaction with collagen fibrils and matrix elements, it appears to play a role in the formation of **endochondral ossification and the fusion and stabilization of the matrix components.**^{12,13} **In noninvasive studies, serum COMP can be used as a risk factor to predict the development of hipographic hip OA.**

Endoglin overexpression has been linked to angiogenesis, inflammation, and wound healing, according to new research.^{14,15} Endoglin is strongly expressed in vascular endothelial cells

and chondrocytes and may be needed to regulate epithelial / mesenchymal changes, which are essential for fetal growth, tissue repair and fibrogenesis.^{16,17}

Osteopontin is a genetic product (OPN) also stored in (Types. Osteopontin is a phosphorylated and sulphated glycoprotein with a molecular weight of 44-66 kDa. linked glycosylated protein) family.¹⁸ In activated T cells, macrophages, osteoblasts, and chondrocytes, osteopontin, one of the collagen-free matrix proteins.¹⁹

Osteopontin is a protein linked to bone remodelling. It appears to play a role in stabilizing osteoclasts in the mineral cortex of bone, according to the study. Since bone lacks calcium if not supplied in the diet, loss of this mineral will lead to bone loss. OPN initiates the process of repetition of the bone by causing the osteoclasts to expand their gigantic boundaries. It is also present in bone, where it helps to prevent kidney stones from forming.

Active C-protein (CRP) is a 23-kDa protein named after its ability to bind pneumococcal proteoglycan C. It belongs to the pentraxin family and is part of the body's ancient immune system. Hs-CRP (a highly sensitive C-protein protein) is a classified receptor for cytokines, particularly interleukin-6 (IL-6). Infection, inflammation, small bowel disease, heart disease, and insulin resistance are all associated with high Hs-CRP levels. While the link between high Hs-CRP levels and rheumatoid arthritis is well known, the link between Hs-CRP and osteoarthritis is more recent.

OBJECTIVES: To estimate biochemical markers in the knee osteoarthritis patients

MATERIAL AN METHODS: The study was conducted in collaboration with AVBRH and JNMC (DMIMS), Sawangi Wardha, in the departments of Biochemistry and Orthopedics at DMMC and SMHRC, Nagpur. Patients in this study were selected using the American College of Rheumatology (ACR) clinical planning process for osteoarthritis.²⁰

Study Design: Total 60 subjects were involved in the study and were categorized into two groups:

Group I: Healthy Volunteer (Control)

Group II: Knee osteoarthritis patients (Study Group)

Study Period: May 2020 to April 2021

Collection of Samples

Synovial fluid was extracted at a rate of 1-2 mL from the affected knee using a sterile knee piercing just before surgery when complete knee arthroplasty, including cell insertion and joint debris, was processed at -80°C for a day. 1 day prior to surgery, blood samples were taken from the same patients, centimeters were taken to remove cells and debris, and

processed to -80°C before use. All of these parameters are estimated using the ELISA commercially available kit: COMP, Endoglin, Osteopontin, and Hs-CRP.

RESULTS

Table 1: Comparison of Plasma COMP, Endoglin, Osteopontin and Hs-CRP between control and study group

Parameters	Control Group	Study Group
COMP ($\mu\text{g/ml}$)	4.08 ± 1.04	9.26 ± 2.42
Endoglin (ng/ml)	4.43 ± 0.3	5.16 ± 0.22
Osteopontin (ng/ml)	67.2 ± 7.7	168.8 ± 15.6
Hs-CRP (mg/L)	1.22 ± 0.23	7.86 ± 5.98

Table 1 displays the data for the healthy volunteers and Knee osteoarthritis patients categories. In this table the levels of plasma COMP, Endoglin, Osteopontin, and Hs-CRP are significantly higher in knee osteoarthritis patients as compared to the healthy volunteers in plasma.

Table 2: Comparison of Synovial fluid COMP, Endoglin, Osteopontin and Hs-CRP between control and study group

Parameters	Control Group	Study Group
COMP ($\mu\text{g/ml}$)	10.18 ± 3.14	18.3 ± 4.5
Endoglin (ng/ml)	5.15 ± 0.36	5.41 ± 0.32
Osteopontin (ng/ml)	65.5 ± 0.6	70.5 ± 1.3
Hs-CRP (mg/L)	1.7 ± 0.9	4.7 ± 3.8

Table 2 shows that the levels of COMP, Osteopontin, and Hs-CRP significantly increased in the study group as compared to the control groups. The level of endoglin is not showed any statistical significant difference in knee osteoarthritis patients as compared to healthy volunteers in synovial fluid.

DISCUSSION

We have confirmed that, as mentioned earlier, COMP standards are age-related. **Differences in age**, BMI, height, presence or intensity of radiographic OA, or the presence of other markers could not explain the racial and sex differences in serum COMP. COMP levels were found to be higher with samples in patients identified as Grades 0 and I, and significantly

decreased in samples from Grades II, III, and IV. According to our findings, COMP levels in synovial fluid from patients with OA are accurate indicators of articular cartilage destruction. In knee patients OA, however, the relationship between endoglin levels in plasma and synovial fluid and the severity of the disease has not been investigated. These findings point to a significant increase in endoglin activity **systematically and spatially in OA primary knee. Endoglin has been found in endothelial cells in synovial tissues in previous studies, and its expression was higher in OA than in normal tissue** implant cells.²¹

Our findings show that the production of osteopontin is increased locally and locally in primary osteoarthritis of the knee. It should be noted that the levels of synovial fluid osteopontin were significantly higher than those found in paired plasma samples. The levels of osteopontin in synovial fluid can be elevated due to the removal of osteopontin from the outer matrix of cells, an increase in its synthesis, or both.

In a population-based study, divided into 845 women in Chingford, **Spector et al.**²² found higher CRP rates in women with naturally occurring knee OA, and higher CRP rates in women with radiographic OA progression over four years of time.

In small samples, **Conrozier et al.**²³ and **Sharif et al.**²⁴ found that low CRP levels were related to OA knee formation, but their findings could not be resolved or contradicted.²⁵⁻²⁸

CONCLUSION

The most common type of arthritis is osteoarthritis. Osteoarthritis (OA) is a very common condition, and its spread is expected to increase dramatically as most people reach the age of 60. These findings indicate a **significant increase in the planned and local development of these biomarkers in early OA knee, as well as the link between disease severity and production, which means they may** be involved in OA pathogenesis. Longitudinal studies with repetitive measurements of these biomarkers in plasma and synovial fluid and their interactions with knee pain OA are necessary to track or predict the clinical course of OA and, ultimately, determine their potential role in determining the best time to participate.

Ethical Approval & Consent

As per international standard or university standard guideline patients consent and ethical approval has been collected and preserved by the authors.

REFERENCES

1. From the Centres for disease control and prevention. Prevalence and impact of arthritis among women- United states, 1989-1991. JAMA 1995;273:1820-1821
2. Praemer A, Furner S, Rice DP. Musculoskeletal condition in the United States. Park Ridge, IIPAmerican academy of orthopaedic surgeons, 1992
3. Lawrence, R., Felson, D., Helmick, C., Arnold, L., Choi, H., Deyo, R. et al. (2008) Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheumatol 58: 26-35.
4. Jr, B. F. P. ., & Federico R. Tewes. (2021). What attorneys should understand about Medicare set-aside allocations: How Medicare Set-Aside Allocation Is Going to Be Used to Accelerate Settlement Claims in Catastrophic Personal Injury Cases. *Clinical Medicine and Medical Research*, 2(1), 61-64. <https://doi.org/10.52845/CMMR/2021v1i1a1>
5. Elders, M. (2000) the increasing impact of arthritis on public health. J Rheumatol 27: 6-8.
6. Bitton, R. (2009) the economic burden of osteoarthritis. Am J Managed Care 15: S230-S235
7. Leigh, J.P., Seavey, W. and Leistikow, B. (2001) Estimating the costs of job related arthritis. J Rheumatol 28: 1647-1654.
8. Wairagade SD, Nagrare AV, Wairagade T, Chandi DH. Efficacy of ayurvedic formulations along with swedana therapy in the management of amavata (Rheumatoid arthritis)-a clinical study. Intern J Cur Res Rev 2020;12(15):79-87.
9. Chopra A, Patil J, Bilampelly V, Relwane J, Tandle HS. Prevalence of rheumatic disease in rural population in western India: A WHO-ILARCOPCORD study. J Assoc Physicians India 2001;49:240-46
10. Daniel, V. ., & Daniel, K. (2020). Diabetic neuropathy: new perspectives on early diagnosis and treatments. *Journal of Current Diabetes Reports*, 1(1), 12–14. <https://doi.org/10.52845/JCDR/2020v1i1a3>
11. Mahajan A, Jasrotia DS, Manhas AS, Jamwal SS. Prevalence of major rheumatic disorders in Jammu. JK Science 2003;5:63-66
12. March LM, Bachmeier CJ. Economics of osteoarthritis: a global perspective. Baillieres Clinical Rheumatology 1997; 11:817-34
13. Neidhart M, Hauser N, Paulsson M, DiCesare PE, Michel BA, Hauselmann IJ. Small fragments of cartilage oligomeric matrix protein in synovial fluid and serum as markers for cartilage degradation. Br J Rheumatol 1997;36:1151-60.
14. Daniel, V., & Daniel, K. (2020). Perception of Nurses' Work in Psychiatric Clinic. *Clinical Medicine Insights*, 1(1), 27-33. <https://doi.org/10.52845/CMI/2020v1i1a5>

15. A.D. Recklies, L. Baillargeon, C. White, Regulation of cartilage oligomeric matrix protein synthesis in human synovial cells and articular chondrocytes, *Arthritis Rheum.* 41 (1998) 997-1006.
16. G.R. Dodge, D. Hawkins, E. Boesler, L. Sakai, S.A. Jimenez, Production of cartilage oligomeric matrix protein (COMP) by cultured human dermal and synovial fibroblasts, *Osteoarthritis Cartilage* 6 (1998) 435-440.
17. Westphal JR, Willems HW, Schalkwijk CJ, et al. A new 180-kDa dermal endothelial cell activation antigen: in vitro and in situ characteristics. *J Invest Dermatol* 1993;100:27-34
18. Torsney E, Charlton R, Parums D, et al. Inducible expression of human endoglin during inflammation and wound healing in vivo. *Inflamm Res* 2002;51:464e470.
19. Barbara NP, Wrana JL, Letarte M. Endoglin is an accessory protein that interacts with the signaling receptor complex of multiple members of the transforming growth factor-beta superfamily. *J BiolChem* 1999;274:584-594
20. Li C, Hampson IN, Hampson L, et al. CD 105 antagonizes the inhibitory signaling of transforming growth factor beta 1 on human vascular endothelial cells. *FASEB J* 2000;14:55-64.
21. Daniel, V., & Daniel, K. (2020). Exercises training program: It's Effect on Muscle strength and Activity of daily living among elderly people. *Nursing and Midwifery*, 1(01), 19-23. <https://doi.org/10.52845/NM/2020v1i1a5>
22. Prince CW, Oosawa T, Butler WT, et al. Isolation, characterization, and biosynthesis of a phosphorylated glycoprotein from rat bone. *J BiolChem* 1987;262:2900-7
23. Denhardt D, Noda M. Osteopontin expression and function: role in bone remodeling. *J. Cell. Biochem., Suppl.* 1998;30—31:92-102
24. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, ChristyW, Cooke TD, Greenwald R, Hochberg M et al. (1986): Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria. Committee of the American Rheumatism Association. *Arthritis Rheum*; 29:1039-1049.
25. Szekanecz Z, Haines GK, Harlow LA, et al. Increased synovial expression of transforming growth factor (TGF)-beta receptor endoglin and TGF-beta 1 in rheumatoid arthritis: possible interactions in the pathogenesis of the disease. *Clin Immunol Immunopathol* 1995; 76:187e194
26. Ranjit S. Ambad, Nishikant Ingole, Pooja A. Sitholay. Use of Tumor Marker and Enzymes in Recurrence and Monitoring Response to Pre and Post Chemotherapy for

Patients with Upper Gastrointestinal Carcinoma. *International Journal of Innovative Research in Medical Science (IJIRMS)* Volume 02 Issue 08 August 2017; 1154-1163.

27. Conrozier T, Chappuis-Cellier C, Richard M, Mathieu P, Richard S, Vignon E. Increased serum C-reactive protein levels by immunonephelometry in patients with rapidly destructive hip osteoarthritis. *Rev Rheum Engl Ed* 1998;65:759–65
28. Sharif M, Elson CJ, Dieppe PA, Kirwan JR. Elevated serum C-reactive protein levels in osteoarthritis [letter]. *Br J Rheumatol* 1997;36:140–1

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