Original Research

Comparative analyses of the effects of Glucosamine and Chondroitin Sulphate Iontophoresis on Cartilage Thickening, Interleukine-6 and Uric Acid in patients with Knee Osteoarthritis

Onigbinde A.T[1], Lasisi K[2], A.B Bello[3], N.R Agbaje[4], Adewuni A.S[5], Adeyemi T[6], Madume A.K[7]

[1]Medical Rehabilitation department, College of Health Sciences, Obafemi Awolowo University, Ife, Nigeria, [2]Physiotherapy department, Osun State University Teaching Hospital, Osogbo, Nigeria, [3]Department of Radiology, Osun State University Teaching Hospital, Osogbo, Nigeria, [4]Department of Laboratory Science, Osun State University Teaching Hospital, Osogbo, Nigeria, [5]Medical services Department, Physiotherapy unit, CBN DTC Abuja, [6]Physiotherapy department, Bowen University, Iwo, Nigeria, [7]Physiotherapy department, Rivers State University Teaching Hospital, Port Harcourt, Nigeria.

How to cite this article: Onigbinde A.T, Lasisi K, A.B Bello et. al. Comparative analyses of the effects of Glucosamine and Chondroitin Sulphate Iontophoresis on Cartilage Thickening, Interleukine-6 and Uric Acid in patients with Knee Osteoarthritis. Indian Journal of Physiotherapy and Occupational Therapy 2023;17(4).

Abstract

This study compared the chondroprotective actions of glucosamine and chondroitin sulphate iontophoresis for cartilage remodeling using Interleukine-6 and Uric Acid as biomarkers. 78 participants with grade II knee OA were randomly assigned to 3 groups. Group one participants received 1g of glucosamine sulphate (GS) while group two received 1g of chondroitin sulphate (CS) through iontophoresis (40mA- min as dosage). Group three participants served as control. The serum concentrations of IL–6 and uric acid were determined while the cartilage thickness was measured using a 7- to 12-MHz linear probe. Descriptive statistics and ANOVA were used to analyze the data. There were significant reductions in the concentrations of interleukin-6 and uric acid at 12th week compared to baseline for the 3 groups ($p = 0.01$). The IL–6 in the CS group was significantly lower compared to that of the GS group ($p = 0.01$). After 12 weeks, across the 3 groups, no significant changes were observed in uric acid concentrations and sonographic features (JSW and ICT). The administration of both drugs significantly reduced inflammatory reactions. However, CS significantly lowered IL–6 compared to GS but there was no significant effect on uric acid concentration. Also, there was no significant change in cartilage thickening after 12 weeks.

Keywords: Osteoarthritis, Glucosamine, Chondroitin Sulphate, Iontophoresis, Interleukine-6, Uric Acid

Introduction

It is increasingly imperative to understand the biochemical and molecular changes involved in the pathogenesis of osteoarthritis (OA), as this may give an insight to providing effective treatment options, and monitoring disease progression or prognosis. Osteoarthritis was considered to be a non-inflammatory joint disease but there are emerging evidences that inflammatory mediators are produced by articular tissues that are implicated in the pathogenesis[1,2,3,4].

Morphological changes in OA include cartilage

Corresponding Author: Onigbinde A.T, Medical Rehabilitation department, College of Health Sciences, Obafemi Awolowo University, Ife, Nigeria.

E-mail: ayotesonigbinde@gmail.com

erosion and synovial inflammation and these have been attributed to changes in series of biochemical factors, including proteolytic enzymes resulting in cartilage breakdown[5]. Although, there is still doubt about biomarkers in relation to stages of osteoarthritis in patients but biomarkers such as interlukin-6 and uric acid have been reported to compromise cartilage degeneration and synovitis leading to greater risk of cartilage loss in patients with OA[6,7]. Increased plasma biomarkers have been considered to be the hallmark of increasing joint inflammatory reactions[4, 8]. Few studies reported that the level of different biomarkers were more in synovial fluid than sera due to their origin from joint cartilages[1,2,3,4].

Amongst drugs which have been speculated to be disease-modifying are glucosamine and chondroitin, but the magnitude of their effects remain unclear and controversial[9]. Both drugs are two molecular building blocks found in articular cartilage, and most clinical research suggested that they have potentiality to retard progression or regenerate damaged cartilage[10]. Most of these trials adopted either the use of oral or intramuscular injections in the administration of glucosamine and chondroitin sulfate whereas there are alternative methods involving the use of electromotive forces in medical rehabilitation field[10,11,12,13].

Biomarkers such as interleukin – 6 and uric acid are known for quantifying joint remodeling and disease progression[12,13]. Specifically, interleukin-6 and uric acid have been reported to be important in monitoring the efficacy and safety of disease modifying OA drugs[14]. The use of electromotive force, especially iontophoresis is becoming a trend in the management of degenerative OA [15]. Electromotive Drug Administration of glucosamine sulphate had been reported to reduce pain, improve physical function and enhance cartilage thickening in patients with knee OA[16]. However, it is unknown if iontophoretic application of glucosamine cream will be more effective than chondroitin sulphate in lowering inflammatory reactions and increasing cartilage regeneration in patients with knee osteoarthritis.

Materials and Methods

78 patients with OA of the knee joint were recruited from the Physiotherapy Departments of Osun State University Teaching Hospital, Osogbo, Osun State, Nigeria. The study period was (June 2020 to July 2021)..

Instruments

The major test instruments and reagents are Glucosamine sulphate cream (glucosamine 8% w/w), (Urah), Chondroitin sulphate cream (Vitabiotics), Ultrasound scanning machine (Model; Landwind Mirror 5China), Electrical stimulator (Model: Endomed 582, India), Elisa plate reader (Model: URIT 660, China) was used for reading optical density (OD) micro plate, Elisa plate washer and incubator (Model: URIT 660, China), Microwell (Model: Accubing, USA) - It is the template with which sample, control and reagent are dispensed, Pipette (Model: 5ml, China), Plasma transfer bottle (Model: 5ml plain) and Chromogen (Model: Accubing, USA).

Methods: Inclusion and Exclusion Criteria

Included were patients with grade II knee osteoarthritis, being 30 years and older, and duration of onset not less than three months. Excluded were patients with history of cardiac disorder with pacemaker, knee surgery, diabetes and nutritional disorder, neuromuscular and other musculoskeletal diseases; and intra articular therapy within two months before the commencement of the study.

Sampling Techniques

107 patients were recruited and purposive sampling technique was used to select 87 participants who met the inclusion criteria. 78 participants completed the study.

Research Design

A randomized controlled trial involving random allocation into 3 groups using Fish-bowl technique.

Procedure for Data Collection

Ethical approval was obtained for the study (UTH/EC/2021/11/549). Informed consent was

obtained from participants. Group 1 participants received 2 FTU (an equivalence of 1g) of GS while group 2 also received 1g of CS, both through iontophoresis. The control group had quadriceps muscle strengthening using resisted exercise (1RM, 10 repetitions and 3 sets); a baseline treatment for the groups. The quantity of weight required for strengthening was determined for each participant by determining 1RM[17]. Each patient flexed and extended the knee joint against the weight for 12 weeks using Standardized procedures[18].

Galvanic current mode was used to deliver the cream through the skin. One gram of GS was placed on positive electrode (being positively charged using Trans-arthral electrode placement technique) for administration of Iontophoresis [40mA-min (2mA x 20minutes)][9,19,20]. The active electrode was placed on the knee side where the participants experienced higher pain intensity. The skin areas where electrodes were fastened were cleansed with methylated spirit (70% alcohol) to minimize the risk of burns[21]. The electrodes were soaked in 3ml of tap water prior to application and held in place by adhesive straps. Interventions were twice a week for 12 weeks.

One gram of Chondroitin Sulphate (CS) cream was placed on the positive electrode of the Electrical stimulator for participants in group 2. Other procedures adopted were as for participants in the GS group. The concentrations of IL–6 in plasma was determined by Enzyme-linked immune sorbent assay (ELISA), involving phases of incubation, washing, dispensing and optical density determination[22]. The concentrations of uric acid in plasma of the participants with knee OA was also determined using ELISA[22]. Cartilage thickness was measured as the distance between the thin hyperechoic line at the synovial space or cartilage interface and the sharp hyperechoic line at the cartilage-bone interface[23]. The cartilage thickness was determined by measuring the lateral and medial joint space width; and intercondylar thickening using Ultrasound machine.

Data Analysis

Descriptive statistics and ANOVA were used to analyze data obtained. Post Hoc Analysis (LSD) was used to determine trend of differences in the groups. The Alpha level was set at $p \leq 0.05$.

Results

The physical characteristics and duration of onset of knee OA are presented in table 1. The radiographic parameters are presented in table 2. There were no significant differences in LJSW, MJSW and ICT of the knee joint within the control, and across the groups (Table 3). The mean and ICT for participants are presented in Table 4.

Table 1: Across- group Comparison of Physical Characteristics

	Glucosamine sulphate		Chondroitin sulphate		Control			
	Mean	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**	**F-ratio**	**p-value**
Age (Years)	59.576	12.423	55.962	9.154	63.654	11.171	3.041	0.005
Weight (Kg)	70.346	7.536	75.500	11.208	76.308	9.711	2.613	0.008
Height (m)	1.585	0.093	1.570	0.946	7.294	29.107	1.042	0.361
BMI (kg/m^2)	28.092	3.116	30.635	4.776	30.644	4.218	3.333	0.042

The serum concentration of interleukin-6 for participants in the GS, CS and control groups are presented in table 4. There were significant differences in interleukin-6 concentrations within the GS, CS and control groups (F= 6.638, P= 0.001, F= 11.936, P= 0.001 and F= 15.666, P= 0.001). The Post hoc analysis showed that there was significant reduction in serum concentration of interleukin-6 at 12th week compared to baseline (p = 0.001) in the groups (Table 5). Table 4, 5, 6 and 7 also presents serum concentrations of uric acid within and across.

Table 2: Within-groups Comparison of Sonographic Parameters

		Baseline		4th week		8th week		12th week			
	SP(mm)	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	F-ratio	p-value
GS	LJSW	2.655	0.715	2.660	0.723	2.671	0.717	2.720	0.705	0.114	0.736
	MJSW	2.555	0.594	2.561	0.593	2.577	0.589	2.587	0.566	0.047	0.828
	ICT	2.847	0.612	2.860	0.601	2.892	0.597	2.937	0.587	0.340	0.561
CS	LJSW	2.722	0.741	2.717	0.750	2.766	0.754	2.782	0.754	0.126	0.724
	MJSW	2.447	0.652	2.473	0.649	2.497	0.644	2.524	0.641	0.204	0.653
	ICT	2.779	0.707	2.785	0.705	3.598	3.856	2.892	0.701	0.396	0.531
Control	LJSW	3.035	0.857	2.920	0.878	3.064	0.854	3.083	0.857	0.173	0.679
	MJSW	2.802	0.788	2.809	0.773	2.830	0.789	2.885	0.874	0.146	0.703
	ICT	3.034	0.869	3.037	0.851	3.063	0.864	3.082	0.861	0.051	0.823

GS: Glucosamine Sulphate CS: Chondroitin Sulphate SP: Sonographic Parameters

Table 3: Across-Groups Comparison of Sonographic Parameters

		Glucosamine Sulphate		Chondroitin Sulphate		Control			
Sonographic Parameters (mm)	Week	Mean	±SD	Mean	±SD	Mean	±SD	F-ratio	p-value
LJSW	Baseline	2.655	0.715	2.722	0.741	3.035	0.857	3.057	0.083
	4^{th}	2.660	0.723	2.774	0.827	2.920	0.878	1.334	0.252
	8^{th}	2.671	0.717	2.766	0.754	3.064	0.854	3.267	0.075
	12^{th}	2.720	0.705	2.782	0.754	3.083	0.857	2.803	0.104
MJSW	Baseline	2.555	0.594	2.447	0.652	2.802	0.788	1.676	0.200
	4^{th}	2.561	0.593	2.508	0.701	2.809	0.773	1.133	0.291
	8^{th}	2.577	0.589	2.497	0.644	2.830	0.789	1.778	0.186
	12^{th}	2.587	0.566	2.524	0.641	2.885	0.874	2.294	0.134
ICT	Baseline	2.847	0.612	2.779	0.707	3.034	0.869	0.807	0.372
	4^{th}	2.86	0.60	2.84	0.78	3.03	0.85	0.357	0.55
	8^{th}	2.892	0.597	3.598	3.857	3.063	0.864	0.070	0.792
	12^{th}	2.937	0.587	2.892	3.701	3.082	0.861	0.512	0.483

Table 4: Within-Groups Comparisons of concentrations of Biomarkers

		Baseline		4th week		8th week		12th week			
	Biomarkers	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F-ratio	p-value
Glucosamine Sulphate	IL-6 (pg/ml)	21.274	3.183	20.727	3.187	20.360	3.321	18.977	3.271	6.638	0.011
	UA(mg/dl)	6.589	1.401	6.104	1.221	5.545	1.134	5.106	1.075	22.010	0.001
Chondroitin Sulphate	IL-6 (pg/ml)	19.611	3.007	18.457	2.839	17.901	2.771	16.984	2.384	11.936	0.001
	UA(mg/dl)	7.062	1.158	6.248	1.049	5.632	1.043	5.121	1.012	46.495	0.00 1
Control	IL-6 (pg/ml)	19.434	2.854	18.840	2.678	17.820	2.524	16.724	2.335	15.666	0.001
	UA(mg/dl)	6.910	1.654	6.270	1.597	5.910	1.537	5.494	1.460	10.628	0.002

Table 5: Within-Group Mean Changes in the Concentrations of Biomarkers

	Biomarkers	I	j	Mean Changes (i-j)	p-value
Glucosamine Sulphate	IL-6 (pg/ml)	1	4	2.297	0.001
	UA (mg/dl)	1	3	1.045	0.001
			4	1.483	0.001
Chondroitin Sulphate	IL-6 (pg/ml)	1	3	1.710	0.028
			4	2.627	0.001
	UA (mg/dl)	1	2	0.814	0.001
			3	1.430	0.001
			4	1.940	0.001
Control	IL-6 (pg/ml)	1	3	1.614	0.031
			4	2.710	0.001
	UA (mg/dl)	1	3	1.000	0.026
			4	1.417	0.002

Significant at $p < 0.05$

***Key**, IL-6; Interleukin-6, UA; Uric Acid. 1: Baseline, 2: 4th week, 3: 8th week, 4: 12th week.*

Table 6: Across-groups Comparisons of concentrations of biomarkers

		Glucosamine		Chondroitin		Control			
	Week	Mean	±SD	Mean	±SD	Mean	±SD	F-ratio	p-value
IL-6 (pg/ml)	Baseline	21.274	3.183	19.611	3.007	19.434	2.854	4.730	0.001
	4th	20.727	3.187	18.332	2.803	18.806	2.646	5.014	0.009
	8th	20.360	3.321	17.901	2.771	17.820	2.524	9.799	0.002
	12th	18.976	3.271	16.984	2.384	16.724	2.335	8.851	0.004
UA (mg/dl)	Baseline	6.589	1.401	7.062	1.158	6.910	1.654	0.656	0.420
	4th	6.104	1.221	6.141	1.123	6.253	1.588	0.156	0.687
	8th	5.545	1.134	5.632	1.043	5.910	1.537	1.085	0.301
	12th	5.106	1.075	5.121	1.012	5.494	1.193	1.324	0.254

Table 7: **Across-Groups Mean Changes in the Concentrations of Biomarkers**

	Biomarkers	I	J	Mean Changes (i-j)	p-value
Baseline	IL-6 (pg/ml)	1	3	1.840	0.033
8th	IL-6 (pg/ml)	1	2	2.459	0.003
			3	2.539	0.002
12th	IL-6 (pg/ml)	1	2	1.993	0.010
			3	2.252	0.004

Discussion

The assessment of changes in Joint Space Width is currently the gold standard to monitor the effects of disease modifying drugs in Osteoarthritis (OA), and reports have also shown cartilage deterioration [24,25.] The current report showed no significant differences in lateral and medial JSW; and ICT following administration of glucosamine and chondroitin sulphate for 12 weeks. These findings contradicted the report of Onigbinde et al, Reginster *et al*. and Dahmers[9,26,27]. This might be due to manual

radiographic assessment adopted in previous studies, that are susceptible to errors[28]. The clinical implication of this current finding is that there was no significant progression in the degeneration of the knee joint of patients with OA after 12 weeks. Also, none of the interventions showed supremacy over the other in slowing down degenerative changes in the articular surfaces.

The current result showed significant reduction in the concentration of interleukin-6 at 12th week compared to that of baseline following administration of glucosamine and chondroitin sulphate iontophoresis. Significant changes were only observed in the interleukin-6 after 4th and 8th week administration of chondroitin and glucosamine sulphate iontophoresis. Generally, there was a significant reduction in IL-6 concentration within each group. Most previous studies documented decrease in serum concentration to be associated with decreasing degeneration[29-32]. Stannus et al and Mukundan et al reported that IL-6 was elevated in knee osteoarthritis in older adults[28,33]. Fraenkel et al., Robinson et al and Rubenhagen et al also reported associations of IL-1β production[34,35,37]. Contrarily, Vlad et al. reported no association between markers of inflammation and osteoarthritis[36]. The significantly lower concentration of serum IL-6 found in this study, implied reduced inflammatory reactions, and this could only be attributed to the effects of the interventions. The uric acid concentrations are also significantly lowered within each group but none of the interventions had supremacy over the other. Kim et al. had earlier reported that serum and urine uric acid was not a risk factor for knee OA progression[38].

Conclusion

Chondroitin sulphate significantly lowered interleukin-6 compared to Glucosamine but both reduced knee joint inflammatory reactions. There was no significant effect on uric acid concentration. Also, there was no progression in the degenerative changes after 12 weeks.

Conflicts of Interest: The authors declared that there is no conflict of interest regarding the publication of this article.

Funding: This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

Ethical Clearance: Ethical approval was obtained for the study from Osun State University Teaching Hospital (UTH/EC/2021/11/549).

References

1. Pelletier, J. P, Martel-Pelletier, J., Abramson, S. B. Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. Arthritis Rheumatology, 2001, 44:1237-47. https://pubmed.ncbi.nlm.nih .gov /11407681.
2. Abramson, S. B., Attur, M., Yazici, Y. Prospects for disease modification in osteoarthritis. National Clinical Practice Rheumatology, 2006, 2: 304–312.
3. Sohn, D. H., Sokolove, J., Sharpe, O., Erhart, J.C., Chandra, P.E., Lahey, L. J. Plasma proteins present in osteoarthritic synovial fluid can stimulate cytokine production via toll-like receptor 4. Arthritis Resource Therapy, 2012, 14: 7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3392793/
4. Berenbaum, F. "Osteoarthritis as an inflammatory disease" Osteoarthritis and Cartilage, 2013, 21 (1): 16–21.
5. Troeberg, L.; Nagase, H. Proteases involved in cartilage matrix degradation in osteoarthritis. Biochim. Et Biophys. Acta, 2012, 1824, 133–14
6. Krasnokutsky, S., Belitskaya-Levy, I., Bencardino, J., Samuels, J., Attur, M., Regatte, R. Quantitative magnetic resonance imaging evidence of synovial proliferation is associated with radiographic severity of knee osteoarthritis. Arthritis Rheumatology, 2011, 63: 2983–2991. https://www.ncbi.nlm.nih. gov/pmc/articles/PMC3183134/
7. Radojcic R Maja, Christian S Thudium, Kim Henriksen, Keith Tan, Rolf Karlsten, Amanda Dudley, Iain Chessell, Morten A Karsdal, Anne-Christine Bay-Jensen, Michel D Crema, Ali Guermazi. Biomarker of extracellular matrix remodelling C1M and proinflammatory cytokine interleukin 6 are related to synovitis and pain in end-stage knee osteoarthritis patients. Pain, 2017 Jul; 158 (7):1254-1263.
8. Hunter, D. J., Guermazi, A. Imaging techniques in osteoarthritis. PM&R, 2012, 4S68– 74.
9. Onigbinde, A. T., Owolabi, A.R., Lasisi, K., Sarah, O.I., Ibikunle, A. F. Symptoms-modifying effects of electromotive administration of glucosamine sulphate amongpatients with knee osteoarthritis Hong Kong Physiotherapy Journal, 2018, 38, No. 1: 1–13.

10. Dhote, V., Bhatnagar, P., Mishra, P. K., Mahajan, S. C., Mishra, D. K. "Intophoresis a Potential Emergence of a Transdermal Drug Delivery Sysytem". Scientia Pharmaceutica, 2012, 80 (1): 1–28.
11. Onigbinde, A.T., Olukola, A. F., Adenike,F. A., Oniyangi, S., Olaitan, O. L. An assessment of hamstring flexibility of subjects with knee osteoarthritis and their age matched control. Clinical Medicine Research, 2013, 2, (issue 6): 121-125.
12. Kraus, V. B. Osteoarthritis year 2010 in review: biochemical markers. Osteoarthritis Cartilage, 2011, 19:346–53.
13. Bijlsma, J.W., Berenbaum, F., Lafeber, F.P. Osteoarthritis: an update with relevance for clinical practice. Lancet, 2011, 377: 2115–26.
14. Onigbinde, A. T., Adesina, O. D., Tarimo, N., Ojoawo. Comparative Effects of a Single Treatment Session Using Glucosamine Sulphate and Methyl Salicylate on Pain and Hamstring Flexibility of Patients with Knee Osteoarthritis. Special Issue: Supplementary Prescribing in Nigeria: A Needy Concept to Promote Clinical Physiotherapy Practice. American Journal of Health Research, 2014Vol. 2, No. 5-1
15. Onigbinde, A.T., Owolabi, A. R., Lasisi, K., Sarah, O. I. Symptoms-modifying Effects of Electromotive Administration of Glucosamine Sulphate among Patients with Knee Osteoarthritis. Hong Kong Physiotherapy Journal. 2017, Vol. 38, No. 1 (2018) 1–13. DOI: 10.1142/S1013702518500075
16. Mabey, T., Honsawek, S. Cytokines as biochemical markers for knee osteoarthritis. World Journal Orthopeadics, 2015, 6(1): 95-105.
17. Kisner, C., Colby,L.A. Therapeutic exercise: foundations and techniques. 5th edition, F.A. Davis Company. 1915 Arch Street, Philadelphia, PA 19103, 2007, www.fadavis.com.
18. Onigbinde, A.T, Olaoye, A.O, Lasisi, K. Clinical and Radiographic Indices as Correlates and Predictors of Self-Reported Physical Functions in Patients with Chronic Knee Osteoarthritis. Rehabilitation Sciences, 2016, 1(1): 9-15.
19. U.S. Patent 530,4380 Glucosamine derivative and liposome containing the same as membrane constituent., 1994, http://www.patentstorm.us/patents/5304380-description.html.
20. Tiziano M. Iontophoresis in pain management. Pract Pain Manage 2014. Available at: www. Practical Pain Management.com.
21. Gazelius, B. Iontophoresis theory htpp//www.perimed.se. 2001. Available at: http//www.perimed.se.
22. Shohichi, K., Toshihiko, S., Junji, C., Chaoying, J., Kazuhiko, I., Jun, K. Interleukin–6 and interleukin–8 levels in serum and synovial fluid of patients with osteoarthritis. Arthritis Resource Therapy, 2009, Pages 71-79
23. Roman-Blas, C. L., Herrero, B. Glucosamine sulfate for knee osteoarthritis: science and evidence-based use Journal of Physical Therapy Science, 2016, (8): 2249–2252.
24. Graig, W. Glucosamine and chondrition for osteoarthritis. Work Safe BC Evidence Based Practise Group, 2003, 1(6):700–3.
25. Carrillon, Y. Imaging knee osteoarthritis. In: Bonnin M, Chambat P, eds. Osteoarthritis of the Knee. Paris: Springer Verlag, 2008, 3–14.
26. Reginster, J., Bruyere, O., Lecart, M., Henroitin. Naturocetic (glucosamine and chondroitin sulphate) compounds as structure-modifying drugs in the treatment of Osteoarthritis. Current Opinion Rheumatology, 2003, 15(5):651–5.
27. Dahmers, S., Schiller, R.M. Glucosamine. America Family Physician, 2008, 1578(4):471–6
28. Mukundan, A., Svetlana, K, Jonathan, S., Steven, B.A. Prognostic biomarkers in osteoarthritis. Current Opinion Rheumatololoy, 2013, 25(1): 136–144.
29. Vilim V, Olejarova M, Machacek S, et al. Serum levels of cartilage oligomeric matrix protein (COMP) correlate with radiographic progression of knee osteoarthritis. Osteoarthritis Cartilage. 2002;10:707–713. https://pubmed.ncbi. nlm.nih.gov/12202123/
30. Sharif M, Kirwan JR, Elson CJ, et al. Suggestion of nonlinear or phasic progression of knee osteoarthritis based on measurements of serum cartilage oligomeric matrix protein levels over five years. Arthritis Rheum, 2004, 50:2479–2488. https://pubmed.ncbi.nlm.nih.gov/15334461/
31. Pelletier, J.P., Raynauld, J.P., Beaulieu, A. DChondrointin sulfate efficacy versus celecoxib on knee osteoarthritis structural changes using magnetic resonance imaging: a 2-year multicentre exploratory study. Arthritis Res Therapy, 2016, 18(1):256.27809891. https://pubmed.ncbi. nlm.nih. gov/20570834/
32. Hoch JM, Mattacola CG, Medina McKeon JM, et al. Serum cartilage oligomeric matrix protein (sCOMP) is elevated in patients with knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis

Cartilage, 2011;19:1396–1404. Important meta-analysis, which showed that serum COMP is elevated in patients with knee osteoarthritis and is sensitive to osteoarthritis disease severity. https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC3962955/

33. Stannus OP, Jones G, Blizzard L, et al. Associations between serum levels of inflammatory markers and change in knee pain over 5 years in older adults: a prospective cohort study. Ann Rheum Dis, 2012 (Epub ahead of print) Serum hsCRP, TNF-α, and IL-6 associated with different measures of worsening knee pain. https://pubmed.ncbi.nlm.nih.gov/22580582/
34. Fraenkel L, Roubenoff R, LaValley M, et al. The association of peripheral monocyte derived interleukin 1beta (IL-1beta), IL-1 receptor antagonist, and tumor necrosis factor-alpha with osteoarthritis in the elderly. J Rheumato, 1998, 25:1820–1826.
35. Rubenhagen R, Schuttrumpf JP, Sturmer KM, Frosch KH. Interleukin-7 levels in synovial fluid increase with age and MMP-1 levels decrease with progression of osteoarthritis. Acta Orthop. 2012, 83:59–64. https://www.ncbi.nlm.nih.gov/pmc /articles/ PMC3278659/
36. Vlad SC, Neogi T, Aliabadi P, et al. No association between markers of inflammation and osteoarthritis of the hands and knees. J Rheumatol. 2011, 38:1665–1670. https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC3193179/
37. Robinson, W.H., Lepus, C.M., Wang, Q. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. National Reviewed Rheumatology, 2016, 12(10):580–59.
38. Go Dong Jin , Dong Hyun Kim, Jie Young Kim, Ali Guermazi, Michel Daoud Crema, David J Hunter, Hyun Ah Kim. Serum uric acid and knee osteoarthritis in community residents without gout: a longitudinal study. Rheumatology, October 2021, Volume 60, Issue 10, Pages 4581–4590, https://doi.org/10.1093/ rheumatology/keab048