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# The Effects Of Surgical Arthroscopy And Intraarticular Medication On The Antioxidant System And Lipid Peroxidation In Knee Osteoarthritis

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**Abstract**

**Aim.** This study aims to evaluate the effects of joint surgery through arthroscopy, intraarticular medication, and antioxidant therapy on the antioxidant system and lipid peroxidation in patients with knee osteoarthritis (KOA). The study examines the ability of high-molecular weight hyaluronan, sodium hyaluronate, and oral Vitamin E to modulate oxidative stress markers in the knee joint.

**Methods and Materials.** There were 60 patients diagnosed with KOA that were divided into four groups according to the type of treatment for this prospective study at the Department of Orthopaedics and Traumatology. Blood and synovial fluid samples collected before and after treatment were evaluated for superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), lipid peroxidation (malondialdehyde, MDA) catalase (CAT). SPSS software was used to perform statistical analysis where the significance level was set at $p<0.05$.

**Results.** Synovial fluid malondialdehyde levels that showed a decreased tendency among treated groups indicated a reduced state of antioxidant activity. However, no significant changes were observed in systemic oxidative stress markers. These findings show that localized antioxidant therapy within the knee can be effective in reducing oxidative stress, therefore, may have implications for nonsurgical treatment of KOA.

**Conclusion.** The results emphasize possible gains made from combining surgical arthroscopy together with antioxidant treatment in managing KOA. By reducing the level of oxidative stress within the knee joint, this combined method can provide a viable solution to improve symptoms and quality of life among KOA patients.

**Keywords:** Knee osteoarthritis (KOA), Oxidative stress, antioxidant therapy, lipid peroxidation

## Introduction

Knee osteoarthritis (KOA) can often cause pain, impairments, and disability. It has far-reaching implications for the daily lives of many people around the world [1]. This condition is caused by the degeneration of cartilage that is supposed to protect the ends of bones from damage. Evidence suggests that knee deterioration has high prevalence rates among elderly individuals and women [2].

The aging process and several other factors have escalated knee osteoarthritis (KOA) into a global public health concern. Osteoarthritis (OA) poses a significant challenge for public health, as it is increasing at an alarming rate with substantial economic consequences and deteriorates quality of life [3]. Considering its significance and priority, preventive measures should be prioritized. However, effective management and control will rely on early detection indicators, precise diagnosis, and the appropriate treatment options [4].

Research typically focuses on methods of drug administration, mechanical means, and sometimes surgical procedures. Therapeutic interventions are designed to reduce pain symptoms, enhance functional abilities, and slow the disease's progression [5]. Physical exercises often complement most therapies since they help maintain the essential body mass for joint protection while taking medications. Otherwise, surgery is required when these remedies are ineffective [6].

Pharmacological approaches include the administration of analgesics along with anti-inflammatory agents used for both inflammation reduction and pain alleviation. Antioxidants may benefit elderly individuals who are prone to poor physical performance, thus putting them at risk of developing osteoarthritis (OA) [7]. Recent studies have targeted the use of antioxidants to prevent damage by OA within cartilage. The effects of antioxidants on mortality or morbidity in diseases remain contradictory, requiring further investigation. For example, antioxidant supplements should be considered therapeutic products and undergo rigorous evaluation before being marketed [8]. These studies were conducted through dietary modification in which the ratio of antioxidant-rich diets was increased while subjects received antioxidant pharmaceutical formulations in addition to a supplement [9]. There have also been studies showing increased or improved muscle strength, facilitation of physical capacities, and reduced likelihood of advancing the disease. All this is derived from the free radical theory of aging, which proposes that oxygen-based free radicals are responsible for age-related cell and tissue damage [10]. Because this issue is crucial, it is necessary to obtain more information from policymakers and physicians so that they can develop effective remedies. The current study has been designed as a comprehensive systematic review that focuses only on articles relevant enough to investigate the effects of antioxidants on KOA and done with utmost care to provide reliable evidence.

## Methods

This study was conducted in the Department of Orthopedics and Traumatology of SDO Faculty of Medicine between January 2005 and May 2005. The diagnosis included knee complaints about pain, clinical and radiographic evidence that the patients had knee osteoarthritis, while those who fulfilled the American College of Rheumatology (ACR) criteria for knee osteoarthritis were eligible.

The research involved a total of 60 knee OA patients where women and men were 24. Inclusion criteria for this group included ACR criterion as well as no pregnancy or desire to become pregnant, no breastfeeding, no drug allergies or hypersensitivities, no severe systemic diseases, absence of conditions that could affect an assessment of the treated knee joint, absence of patients who received intraarticular therapy in the study knee within a three month period prior to entry in that case series, and finally exclusion due to arthroscopic surgery performed in last three years (figure 1).

The patients were randomly placed into four groups. Anamnesis has been specified in detail along with systemic physical examination and examination of the motion system. Haematological tests including routine blood biochemistry erythrocyte sedimentation rate c-reactive protein rheumatoid factor levels blood type coagulation time complete urine analysis have been carried out for each patient before surgery. All participants underwent a bilateral X-ray examination of their knees; posteroanterior chest radiograph (CXR) and electrocardiography were added for age over 40.

After arthroscopy treatment first group received high molecular weight hyaluronan (Hylan G-F 20) at weekly intervals after arthroscopy with three doses given per person. Furthermore, Hylan G-F-20 used oral vitamin E (Grandpherol®), taken once daily at a dose of 400 IU for three weeks. This control group was not treated with any type of intraarticular therapy after arthroscopy. Sodium hyaluronate was injected as a dose of 2 ml into the joint cavity after arthroscopy weekly basis for five consecutive times in patients in the fourth group.

Before and one week after the last injection, blood samples and synovial fluid were collected to determine the SOD, CAT, GSH-Px, and MDA content.

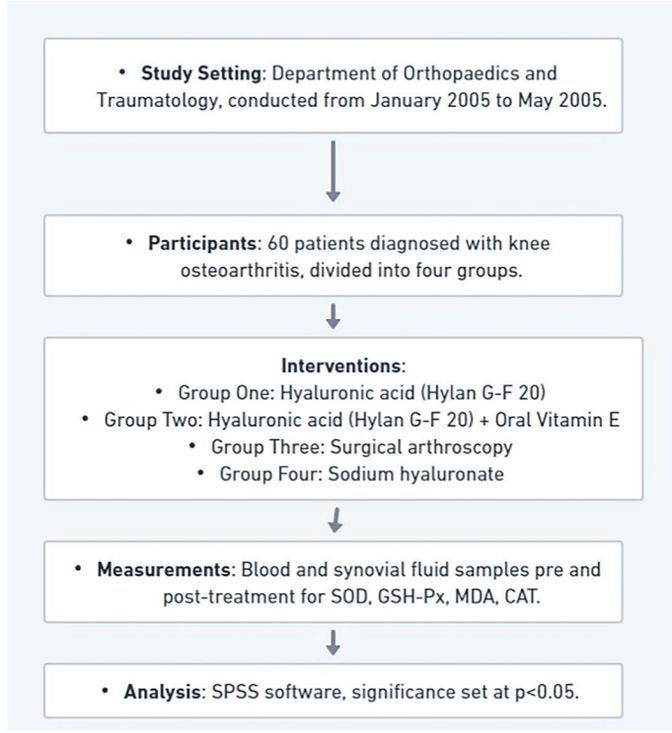


**Figure 1** - Study Design

The fasting period started at midnight before the operation. Immediately prior to surgery, the leg to be operated on was shaved from the knee to the thigh. The arthroscopic intervention was performed under general or spinal anaesthesia in an antiseptic operating room. All patients had debridement arthroscopically, Kirchner wire used while microfracture K wires during entry into knee joint through the anterolateral approach described by the Watanabe anatomical approach described by the Watanabe versatile access route described by the Watanabe anterolateral approach as told by Watanabe through which cartilage lesions seen during arthroscopy were classified according to the Outerbridge classification system.

At our institution, this study was approved by the local institutional review board (IRB) meeting the ethical standards described in the Declaration of Helsinki. Furthermore, written informed consent has been obtained from all individuals participating in this experiment. The reference number and name will be provided on request.

Data analysis using SPSS software version 25 windows was performed for descriptive statistics of demographic, clinical biochemical data, including Wilcoxon test and other tests within each treatment group were done; p-value $<0.05$ is considered significant statistically.

## Results

This is an intricate study that examines in detail various treatments for knee osteoarthritis among 60 patients divided into four groups. The study focusses mainly on the classifications of cartilage lesions and assessing biochemical markers before and after treatment.

A total of 60 people participated in this investigation who were further divided into four groups: Group One (Hylan G-F 20), Group Two (Hylan G-F 20 plus oral vitamin E), Group Three (surgical arthroscopy) and Group Four (Na-Hyaluronate). In group one, Hylan G-F20 was used to provide fifteen cases (10 women and five males) with average age determined to be fifty three point two six.

**Table 1** Patient Demographics and Distribution Across Treatment Groups

| Treatment Group | Therapy Applied | Male Patients | Female Patients | Average Age | Total Patients |
|---|---|---|---|---|---|
| Group 1 | Hyalan G-F 20 | 5 | 10 | 53.26 | 15 |
| Group 2 | Hyalan G-F 20 + Oral Vitamin E | 6 | 9 | 52.93 | 15 |
| Group 3 | Surgical Arthroscopy | 7 | 8 | 52.13 | 15 |
| Group 4 | Na-Hyaluronate | 7 | 8 | 51.8 | 15 |
| **Total** | | 25 | 35 | 52.53 | 60 |

**Note:** The patient population comprised 60% females and 40% males, with the youngest participant being 40 years old and the oldest 68 years old. There was no statistically significant difference in the average age across treatment groups (p>0.05).

**Table 2** Grading and Distribution of Cartilage Lesions by Treatment Group and Joint Structure

| Joint Structure | Grade-1 Lesions | Grade-2 Lesions | Grade-3 Lesions | Grade-4 Lesions | Total Lesions |
|---|---|---|---|---|---|
| Patella | 4 | 28 | 35 | 11 | 78 |
| Femur Medial Condyle | 3 | 41 | 44 | 14 | 102 |
| Femur Lateral Condyle | 2 | 11 | 10 | 3 | 26 |
| **Femur Trochlea** | 4 | 38 | 38 | 4 | 84 |
| **Tibia Medial Condyle** | 5 | 25 | 28 | 3 | 61 |
| **Tibia Lateral Condyle** | 2 | 10 | 11 | 2 | 25 |
| **Total** | 20 | 153 | 166 | 37 | 376 |

Similarly, the second group consisted of 15 subjects (9 women and six men) with a mean age of fifty two point nine three receiving Hylan G-F 20 plus oral vitamin E. The third group had fifteen patients [8 women + 7 men] whose average age was fifty two point one three. Finally, Na-hyaluronate was administered at its recommended dose to 15 cases [8 females +7 males] aged about fifty and one point eight as illustrated in Table I below. This distribution demonstrates an equitable representation of gender within the sample population across all groups with middle-aged being primarily affected by knee arthritis of the knee (Table 1).

Therefore, it is important for us also to test for severity as well as distribution so that we can get insights into how therapeutic interventions affect those suffering from osteoarthritis of the knees during our investigation. These grades were used in diagnosing about three hundred seventy-six cartilage injuries present in 60 patients according to Outerbridge's grading system. This discovery reveals that there are more osteoarthritic changes that occur in the medial femoral condyle compared to any other site within the knee joint.

**Table 3** Pre- and Post-Treatment Biochemical Values in Blood and Synovial Fluid

| Treatment Group | Parameter | Pre-Treatment (Blood) | Post-Treatment (Blood) | Pre-Treatment (Synovial Fluid) | Post-Treatment (Synovial Fluid) |
|---|---|---|---|---|---|
| **Group 1** (Hyalan G-F 20) | CAT (U/g) | 9.144 | 9.128 | - | - |
| | MDA (µmol/L) | 35.95 | 35.96 | 0.3108 | 0.1066* |
| | SOD (U/g) | 1761.9 | 1761.92 | - | - |
| | GPX (U/g) | 74.85 | 74.82 | - | - |
| **Group 2** (Hyalan G-F 20 + Vitamin E) | CAT (U/g) | 10.854 | 10.861 | - | - |
| | MDA (µmol/L) | 33.48 | 33.43 | 0.4928 | 0.334* |
| | SOD (U/g) | 2174.33 | 2174.33 | - | - |
| | GPX (U/g) | 87.43 | 87.44 | - | - |
| **Group 3** (Surgical Arthroscopy) | CAT (U/g) | 8.436 | 8.397 | - | - |
| | MDA (µmol/L) | 32.48 | 32.85 | 0.9302 | 0.928 |
| | SOD (U/g) | 1691.8 | 1691.85 | - | - |
| | GPX (U/g) | 85.03 | 85.04 | - | - |
| **Group 4** (Na-Hyaluronate) | CAT (U/g) | 12.92 | 12.11 | - | - |
| | MDA (µmol/L) | 34.42 | 34.52 | 1.9308 | 1.6813* |
| | SOD (U/g) | 2147.45 | 2146.8 | - | - |
| | GPX (U/g) | 112.91 | 112.25 | - | - |

**Table 4** Statistical Analysis of Biochemical Marker Changes Pre- and Post-Treatment

| Treatment Group | Biochemical Marker | Pre-Treatment Average | Post-Treatment Average | p-Value | Statistical Significance |
|---|---|---|---|---|---|
| **Group 1** (Hyalan G-F 20) | Catalase (CAT) U/g | 9.144 | 9.128 | >0.005 | No |
| | Malondialdehyde (MDA) µmol/L | 35.95 | 35.96 | >0.005 | No |
| | Superoxide Dismutase (SOD) U/g | 1761.9 | 1761.92 | >0.005 | No |
| | Glutathione Peroxidase (GPX) U/g | 74.85 | 74.82 | >0.005 | No |
| | **MDA in Synovial Fluid** µmol/L | 0.3108 | 0.1066 | <0.005 | **Yes** |
| **Group 2** (Hyalan G-F 20 + Vitamin E) | MDA in Synovial Fluid µmol/L | 0.4928 | 0.334 | <0.005 | **Yes** |
| **Group 3** (Surgical Arthroscopy) | MDA in Synovial Fluid µmol/L | 0.9302 | 0.928 | >0.005 | No |
| **Group 4** (Na-Hyaluronate) | MDA in Synovial Fluid µmol/L | 1.9308 | 1.6813 | <0.005 | Yes |

The area around the lunate surface, patella and lateral aspect femoral trochlea are some important areas that easily wear out through common biomechanical stress points in the knee joint. Table 2 shows such classifications and therefore helps to guide which treatment is best for different degrees of cartilage damage.

As a result, our extensive biochemistry study aimed to determine systemic as well as local biochemical responses associated with the therapies employed herein. Additionally, no significant differences were observed in catalase, malondialdehyde, superoxide dismutase, and glutathione peroxidase levels before and after blood samples from all subjects in all groups. Therefore, this shows that any treatment does not have much impact on general oxidative stress or the antioxidant capacity of an organism. In contrast, Groups 1, 2 and 4 had reduced malondialdehyde in their synovial fluids during the post-treatment period indicating increased localised oxidative stresses within their knee joints. These findings presented in Table 3 provide a clear target for local therapy rather than systemic biochemical changes that result in redox injury within the affected joint.

A thorough statistical analysis was performed to assess how the treatments had an impact. It is possible that intraarticular knee injections treatment may help reduce lipid peroxidation, which could be as a result of suppressing cellular damage and thus nitric oxide (NO) production through increased enzymatic activities. The findings imply that such therapeutic strategies can directly influence markers of oxidative stress within the knee joint, but not the systemic biochemical parameters (Table 4). These discoveries highlight the localised nature of the therapy and its potential as a non-intrusive method for treating osteoarthritis of the knee. This method targets oxidative stress in order to prevent cartilage degradation, it is a direct way to slow down arthritis progression from occurring in knees.

In conclusion, these detailed observations have demonstrated how different treatments affect knee osteoarthritis at various levels. However, there is a significant reduction in synovial fluid malondialdehyde after therapy within the chosen groups, indicating another way to attenuate local oxidative stresses from inside the knee joint itself, apart from some notable findings about systemic biochemical markers, among others.

## Discussion

According to this study, the use of antioxidants in a specific area is effective in treating oxidative stress in the knee joint, which is one of the most important causes of knee osteoarthritis (OA). Although there were no significant systemic changes in oxidative markers; this shows that treating joints with antioxidants can reduce the levels of malondialdehyde in synovial fluid - a biomarker of local tissue damage caused by free radicals - and thus relieve pain locally. In other words, it means that this treatment can focus on particular symptoms or sites only where they occur without affecting general health conditions. This implies that although very little happens elsewhere apart from around where an operation has been done, still much relief could come about through dealing with oxidation changes near an affected area. Therefore, further research is needed on how best surgery and nonsurgical methods can be combined to improve quality of life among these patients.

Furthermore, it is important to note that there were no significant changes in systemic oxidative stress markers. Therefore, the conclusion is made that antioxidant and anti-inflammatory properties are more specific for local organs such as the knees than the whole body [13]. This suggests that there may be a treatment modality which provides relief and therapeutic benefits at the source of pain and dysfunction associated with OA without affecting any systemic biomarkers of oxidative stress. Consequently, addressing localised pathways to reduce oxidative stress within the knee joint could lead to the development of therapies targeting symptoms caused by KOA specifically. In addition, it opens up possibilities for therapeutic strategies aimed at reducing the systemic side effects that often accompany many pharmacological options [14]. Consequently, all of these point to the need for effective treatment modalities not only against localised pathologies linked to osteoarthritis but also safe without unwanted systemic consequences.

Comparing these results with other studies helps to unravel how antioxidants help to manage OA. Although some researchers have questioned whether antioxidants such as vitamin E can effectively treat osteoarthritic signs, others claim that their combination with hyaluronic acid treatments may cause a significant decrease in levels of oxidative stress within knee joint. Thus, combined therapy may improve its efficacy [15]. In this sense, these data brings out issues on the complexity of osteoarthritis and show what can be improved through combining several forms of therapy. Therefore, differences between the results of the trials have arisen because OA has proven quite complicated as a disease; therefore, one needs to consider a wide range of treatments directed towards different substrates [7].

Our analysis revealed that hyaluronic and vitamin E have intricate curative actions within the KOA oxidative stress mechanisms of KOA [16]. This means that the pathogenesis of KOA is based on oxidative stress, resulting in cartilage degradation and facilitating inflammation; therefore, antioxidants can be considered as potential modulatory agents for disease progression [17]. Moreover, HA is viscoelastic in addition to being a knee joint lubricant that may decrease mechanical loading in order to generate a suitable milieu. It aims to decrease stress levels by reducing ROS production. Moreover, this could make it more secure when combined with a lipid-soluble antioxidant such as Vitamin E. In addition, in this case, Vitamin E acts as an antioxidant molecule that neutralises free radicals, and inhibits chain propagation reactions that lead to lipid peroxidation hence preserving cell integrity in joint tissues against oxidative challenges that would otherwise affect articular cartilage due to oxidation [18].

However, certain restrictions must be kept in mind in order to fully comprehend the scope and relevance of our findings. Additionally, we note that despite having enough weakness size to make some tentative conclusion based on our data on this condition we realize it was not representative of all patients with KOA and could not incorporate all possible cases throughout its spectrum. Different individuals manifest various grades of severity of this ailment, as well as different responses to treatment modalities applied for its control. Furthermore, since it was a short study, we did not know if these therapies were effective or influenced the progression of KOA after this period. Therefore, longer follow-up studies are required than what was used here, noting changes in local and body-wide indicators of oxidative stress over time to establish whether such treatments are sustainable for improving health outcomes improvement or improving quality enhancement respectively [19].

Additionally, one should consider carefulness about generalisations among dissimilar affected populations by osteoarthritis, various stages of diseases, and other joints except knee also. This is because OA is a complex condition that arises from various aetiology factors such as genetic background,

lifestyle components that include everyday movement patterns and types of mechanical stresses people undergo among many others which can interact differently with the findings of this research [20]. More patients suffering from osteoarthritis at all stages from common sites including hands and hips, should be enrolled for future analysis to establish these observations. Furthermore, in addition to confirming the present results, they would help to understand how hyaluronic acid and Vitamin E function more fully by providing a clearer idea of the conservative treatment approaches discussed against osteoarthritis [7]. In another recent study, these authors reported on the comparative effects of different treatments for osteoporosis bone loss on joint pain and showed ways through which bone health indices involving the vertebrae or hip could be improved [16].

Treatment for osteoarthritis of the knee can be further established by this study. Furthermore, it discloses that antioxidants can decrease oxidative stress within the knee joint. These findings imply that medical interventions are possible and therefore more research looking into treatment approaches, combinatorial therapies, and quality of life improvement in KOA patients. Consequently, this can lead to change in clinical practice to more targeted symptom relief and improved joint function while minimising systemic side effects which are currently prevalent with a wider spectrum of adverse effects. As such, these results support the inclusion of antioxidant therapy in KOA guidelines pending future studies.

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## References

1. Litwic A, Edwards MH, Dennison, EM, Cooper C. Epidemiology and burden of osteoarthritis. *British Medical Bulletin*. 2013; 105: 185-199. https://doi.org/10.1093/bmb/lds038
2. Canter PH, Wider B, Ernst E. The antioxidant vitamins A, C, E and selenium in the treatment of arthritis: A systematic review of randomized clinical trials. *Rheumatology (Oxford)*. 2007; 46(8): 1223-1233. https://doi.org/10.1093/rheumatology/kem116
3. Hsiao AF, Lien YC, Tzeng IS, Liu CT, Chou SH, Horng YS. The efficacy of high- and low-dose curcumin in knee osteoarthritis: A systematic review and meta-analysis. *Complementary Therapies in Medicine.* 2021; 63: 102775. https://doi.org/10.1016/j.ctim.2021.102775
4. Suantawee T, Tantavisut S, Adisakwattana S et al. Oxidative stress, vitamin E, and antioxidant capacity in knee osteoarthritis. *Journal of Clinical and Diagnostic Research.* 2013; 7(9): 1855-1859. https://doi.org/10.7860/JCDR/2013/5802.3333
5. Atabaki M, Shariati-Sarabi Z, Tavakkol-Afshari J, Mohammadi M. Significant immunomodulatory properties of curcumin in patients with osteoarthritis; a successful clinical trial in Iran. *International Immunopharmacology.* 2020; 85: 106607. https://doi.org/10.1016/j.intimp.2020.106607
6. Buck AN, Vincent HK, Newman CB et al. Evidence-Based Dietary Practices to Improve Osteoarthritis Symptoms: *An Umbrella Review. Nutrients.* 2023: 15(13): 3050. https://doi.org/10.3390/nu15133050
7. Grässel S, Muschter D. Recent advances in the treatment of osteoarthritis. *F1000Research.* 2020; 9 (F1000 Faculty Rev): 325. https://doi.org/10.12688/f1000research.22115.1
8. Rahimnia AR, Panahi Y, Alishiri G, Sharafi M, Sahebkar A. Impact of Supplementation with Curcuminoids on Systemic Inflammation in Patients with Knee Osteoarthritis: Findings from a Randomized Double-Blind Placebo-Controlled Trial. *Drug Research (Stuttg)*. 2015; 65(10): 521-525. https://doi.org/10.1055/s-0034-1384536
9. Ozon EA, Iuga IDM, Mititelu M et al. Pharmacotechnical, Physico-Chemical, and Antioxidant Evaluation of Newly Developed Capsule Formulations. *International Journal of Molecular Sciences*. 2023; 24(14): 11426. https://doi.org/10.3390/ijms241411426
10. Kulkarni PD, Damle ND, Singh S et al. Double-blind trial of solid lipid Boswellia serrata particles (SLBSP) vs. standardized Boswellia serrata gum extract (BSE) for osteoarthritis of knee. *Drug Metabolism and Personalized Therapy.* 2020; 35(2): 20200104. https://doi.org/10.1515/dmpt-2020-0104
11. Bhattacharya I, Saxena R, Gupta V. Efficacy of vitamin E in knee osteoarthritis management of North Indian geriatric population. *Therapeutic Advances in Musculoskeletal Disease.* 2012; 4(1): 11-19. https://doi.org/10.1177/1759720X11424458
12. Tan BL, Norhaizan ME, Liew WP, Sulaiman Rahman H. Antioxidant and Oxidative Stress: A Mutual Interplay in Age-Related Diseases. *Frontiers in Pharmacology.* 2018; 9: 1162. https://doi.org/10.3389/fphar.2018.01162
13. 13. Hu HC, Lei YH, Zhang WH, Luo XQ. Antioxidant and Anti-inflammatory Properties of Resveratrol in Diabetic Nephropathy: A Systematic Review and Meta-analysis of Animal Studies. *Frontiers in Pharmacology.* 2022; 13: 841818. https://doi.org/10.3389/fphar.2022.841818
14. Ansari MY, Ahmad N, Haqqi TM. Oxidative stress and inflammation in osteoarthritis pathogenesis: Role of polyphenols. *Biomedicine & Pharmacotherapy.* 2020; 129: 110452. https://doi.org/10.1016/j.biopha.2020.110452
15. Nejadhosseinian M, Djalalinia S, Haerian H et al. The effects of antioxidants on knee osteoarthritis: A systematic review and meta-analysis. *Frontiers in Nutrition.* 2022; 9: 1026450. https://doi.org/10.3389/fnut.2022.1026450
16. 16. Menekşe S, Menekşe D. Comparison of the efficacy of oral and parenteral bisphosphonates in patients with postmenopausal osteoporosis: A single-center, retrospective clinical study. *Turkish Journal of Clinics and Laboratory.* 2022; 13(1): 146-152. https://doi.org/10.18663/tjcl.764506
17. Liu L, Luo P, Yang M, Wang J, Hou W, Xu P. The role of oxidative stress in the development of knee osteoarthritis: A comprehensive research review. *Frontiers in Molecular Biosciences.* 2022; 9: 1001212. https://doi.org/10.3389/fmolb.2022.1001212
18. Vincent HK, Percival SS, Conrad BP, Seay AN, Montero C, Vincent KR. Hyaluronic Acid (HA) Viscosupplementation on Synovial Fluid Inflammation in Knee Osteoarthritis: A Pilot Study. *The Open Orthopaedics Journal.* 2013; 7: 378-384. https://doi.org/10.2174/1874325001307010378
19. Papageorgiou SN. Visualising the results of clinical trials to draw conclusions. *Journal of Orthodontics.* 2022; 49(2): 240-243. https://doi.org/10.1177/14653125221101911
20. Kokkotis C, Moustakidis S, Baltzopoulos V, Giakas G, Tsaopoulos D. Identifying Robust Risk Factors for Knee Osteoarthritis Progression: *An Evolutionary Machine Learning Approach. Healthcare (Basel).* 2021; 9(3): 260. https://doi.org/10.3390/healthcare9030260