Aus der Klinik und Poliklinik für Orthopädie und Unfallchirurgie der Universität zu Köln
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Vergleichende Untersuchung der Osteopontinwerte im Plasma vor und nach einer Kniegelenkersatzoperation bei Patienten mit schwerer idiopathischer Osteoarthritis

(Comparative Study of Plasma Osteopontin Levels before and After Knee Joint Replacement Surgery in Patients with Severe Idiopathic Osteoarthritis)

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List of Abbreviations

(ACL)	Anterior Cruciate Ligament
(ACR)	American College of Rheumatology
(ADAMTS-5)	A disintegrin and metalloproteinase with thrombospondin motifs 5
(BMI)	Body Mass Index
(BMP-7)	Bone morphogenetic protein-7
(CIA)	Collagen-induced arthritis
(COL2A1)	Collagen Type II Alpha 1 Chain
(CRP)	C-Reactive Protein
(CTX-II)	C-terminal telopeptide
(ECM)	Extracellular matrix
(Eta-1)	Early T cell activation gene-1
(GBD)	Global Burden of Diseases
(HDL)	High-density lipoprotein
(IL1)	interleukin 1
(IL-6)	Interleukin-6
(iNOS)	Inducible nitric oxide synthase
(MIA)	Mono sodium iodoacetate
(MJOA)	Multiple-joint Osteoarthritis
(MMP-13)	matrix metalloproteinase-13
(MMP-9)	matrix metalloproteinase-9
(NF-κB)	Nuclear factor kappa B
(NHANES)	Korean National Health and Nutrition Examination Survey
(NO)	Nitric oxide
(NSAIDs)	Nonsteroidal Anti-Inflammatory Medications

(OA)	Osteoarthritis
(OCN)	Osteocalcin
(OPN)	Osteopontin
(PGE2)	Prostaglandin E2
(QOL)	Quality Of Life
(RUNX2)	RUNX Family Transcription Factor 2
(SIBLING)	Small integrin-binding ligand N-linked glycoproteins
(SMC)	Smooth muscle cells
(SPP1)	Secreted phosphoprotein 1
(TENS)	Transcutaneous electrical nerve stimulation
(TJA)	Total joint arthroplasty
(TNF-a)	Tumor necrosis factor-alpha
(TRAP)	Tartrate-resistant acid phosphatase

1. Summery

1.1. Abstract

Osteoarthritis (OA) causes pain, disability, and worse quality of life. Its etiology and pathogenesis are unknown, although OA is widespread. Despite being a cytokine, hormone, and extracellular matrix (ECM) glycoprotein, OPN has been linked to greater cartilage mRNA expression in OA and joint degeneration patients. **Method:** Thirty patients with endstage osteoarthritic of the knee joints who were scheduled for knee replacement surgery were included. Using an enzyme-linked immunosorbent assay (ELISA), the plasma levels of OP (Osteopontin) were assessed before and six months after the implantation of a total knee replacement. All patients were subjected to full history, clinical examinations and laboratory investigation. **Results:** Our research included 30 patients, 12 of them were men. The population's mean age was 71.5 years, and their BMI is 29.9. In patients undergoing knee surgery, pre-operative plasma OPN levels varied from 14.3 ng/ml to 241.2 ng/ml with a mean level of 73.4 ng/ml; however, six months after surgery, the mean level increased to 84.9 ng/ml. **Conclusion:** Plasma OPN levels were examined before and six months after total knee replacement surgery in this study. Even though OPN levels rose up, the difference was not statistically significant. This suggests that surgery may cause complex biological processes that change OPN levels.

Key Words: Osteopontin, Osteoarthritis, knee.

1.2. Zusammenfassung

Die vorliegende Studie untersuchte die Plasma-OPN-Spiegel vor und nach sechs Monaten einer Kniegelenkersatzoperation bei 30 Patienten mit schwerer idiopathischer Kniearthrose. Durch die Ergebnisse dieser Studie erwarten wir, zukünftige Vorteile für Patienten mit der oben genannten Erkrankung zu bieten sowie ein besseres medizinisches Verständnis der Reaktion der Osteopontin-Plasmaspiegel im Zusammenhang mit Kniegelenkersatzoperationen und deren immunologischer Korrelation zu erreichen. Während ein Anstieg der OPN-Spiegel beobachtet wurde, war dieser statistisch nicht signifikant, was darauf hindeutet, dass der chirurgische Eingriff komplexe biologische Reaktionen auslösen kann, die die OPN-Spiegel beeinflussen. Zukünftige Forschung sollte längsschnittliche Studien mit größeren Stichproben umfassen, um Trends in den Veränderungen der OPN-Spiegel zu identifizieren und deren Rolle als Biomarker für den Krankheitsverlauf und die Behandlungsergebnisse zu bestimmen. Zudem sollten Kontrollgruppen einbezogen werden, um die spezifische Auswirkung der Kniegelenkersatzoperation auf die OPN-Spiegel zu ermitteln.

2. Introduction

One of the most prevalent and disabling degenerative joint disorders in the world is knee osteoarthritis (OA), which affects 25% of patients (between adults ≥ 45) and limits their ability to perform important daily activities for 80% of them.[1] Although cartilage deterioration and osteophyte production continue to be the morphological characteristics of knee OA, the condition is now understood to be a whole-organ pathology that affects the meniscus and synovium in addition to other tissues throughout the knee joint. Pain, stiffness, and mobility limitation are common complaints, and its clinical presentation is varied.[2]

Even though OA is quite widespread, little is known about its origin and pathophysiology. In addition, there is no known cure, therefore therapy focuses on managing symptoms, with the exception of severe instances that are needed for joint replacement surgery.[3]

OPN is a cytokine, hormone, and extracellular matrix (ECM) glycoprotein with several recognized activities; nevertheless, it has been shown in earlier research that people with OA and joint degeneration had higher levels of mRNA expression in cartilage.[4] This is considered to be caused by an immunological response that inflammation triggers.[5] Release from the extracellular matrix (ECM), cartilage, or bone, inflammation, or MMP or thrombin cleavage might raise it in OA patients. Epithelial, smooth muscle, and endothelial cells release it. MMP-2, 3, 7, and 9 in particular are known to cleave OPN. Multiple protein cleavage sites reveal binding sites, controlling OPN.[4,6,7]

Previous research has shown that thrombin cleaves OPN at certain locations believed to be crucial in the pathophysiology of OA.[8] This kind of OPN has a role in a number of comparable pathophysiologic disorders as well as the inflammatory cascade.[8] OPN that has been thrombin-cleaved is higher in advanced stages of OA and is recognized to have a significant role in the development of the disease.[8] OPN cleaved by thrombin may be detected in OA patients' synovial fluid and is a useful indicator of the severity and development of the condition.[9,10] Additionally, it has been suggested that this fragment contributes to the formation of thrombotic problems in atherosclerotic plaques, offering a potential link to the consequences of coagulopathy in OA patients.[11]

It was proposed that circulating levels of OPN may be higher in patients having total joint arthroplasty (TJA) owing to severe OA than in healthy controls. These biomarkers may be measured to better understand the pathophysiology of OA and the early post-surgical alterations that follow TJA. Additionally, the circulating concentrations of these biomarkers may

have predictive significance in the preoperative risk classification of these individuals.
The results of this study aim to provide future benefits for patients with knee osteoarthritis, as well as a better medical understanding of the response of osteopontin plasma levels in relation to knee replacement surgery and its immunological correlation.

2.1. Osteoarthritis

2.1.1. Definition and intro to osteoarthritis:

Osteoarthritis (OA), the most prevalent joint pathology associated with aging that affects all joint components. Articular cartilage loss is the primary characteristic of OA, coupled with alterations in the bone, muscles, capsule, ligaments, synovium, and menisci that are present in joints (Figure 1).[12] Until the second half of the eighteenth century, doctors did not identify OA[13], and additional nomenclature confusion delayed identification because it was mistakenly regarded as the same condition as rheumatoid arthritis.[14]

Symptomatic OA affects 18.0% of women and 9.6% of men over 60 worldwide, according to estimates.[15] Most adults over 65 have radiographic evidence of OA, and 80% over 75 have.[16]

The diagnosis of osteoarthritis is generally done based on an X-ray.[17] Loss of cartilage, osteophyte growth, subchondral bone abnormalities, and meniscal modifications are some of the structural damages to the joint that may be observed on MRI but can also be visible on radiography in certain cases.[18,19] Joint pain could also follow these changes. In OA, the disease normally progresses gradually and may take many years to manifest. The intensity and symptoms of this illness might subsequently deteriorate as a result of its stages or gradual progression over time.[20] OA may be categorized as primary (idiopathic) or secondary based on the identification of known causal causes, such as trauma, surgery on the joint structures, and malformed joints at birth.[21]

2.1.2. Etiology:

It is mostly unknown what causes osteoarthritis (OA). The development of OA is not caused by a single illness state but rather by a complicated disorder that is linked to several risk factors. While the genes that cause OA are mostly understood, constitutional and biomechanical risk factors play a significant role in its onset and progression.[22,23] Several diagnostic techniques, including a radiographic and clinical examination combination, are used to identify OA.[24]

2.1.3. Prevalence and incidence:

Although the majority of studies have focused on OA at particular locations, others have offered information on OA prevalence and incidence more broadly. In the globe, 240 million people are thought to have symptoms of OA, with 10% of men and 18% of women in this age group affected.[25] According to current GBD estimates, the age-standardized point prevalence and annual incidence rate of symptomatic, radiographically confirmed hip and knee OA were 3754.2 and 181.2 per 100,000, respectively.[26] These numbers represent 9.3% and 8.2% increases since 1990. Several countries have carried out population-based research on the prevalence and incidence of OA. A large survey of over-50s in England found that over half had OA in at least one joint, including the knee, hip, hand, and foot.[27] Based on screening questions that fulfilled American College of Rheumatology (ACR) clinical criteria, a recent survey research of people above the age of 20 in Spain discovered that 29% of people had OA at one or more sites.[28] Using a large nationally representative primary care database, researchers in the United Kingdom (UK) revealed that between 1997 and 2017, there were 494,716 incident instances of clinical OA, or 6.8 incidences per 1000 person years.[29] A further research that made use of these data found that, among patients above the age of 45, the yearly age- and sex-adjusted incidence rate for clinical OA rose from 29.2 to 40.5 per 1000 person years from 1992 to 2013.[30]

Multiple-joint OA (MJOA), which has been described in at least 10 distinct ways, has also generated attention.[31] It has been challenging to get an agreement on the prevalence of MJOA due to this diversity. Prevalence estimates were discovered in a systematic study to range from 5% to 25%. Comparing MJOA to single joint involvement, worse OA-related outcomes have generally been seen.[32]

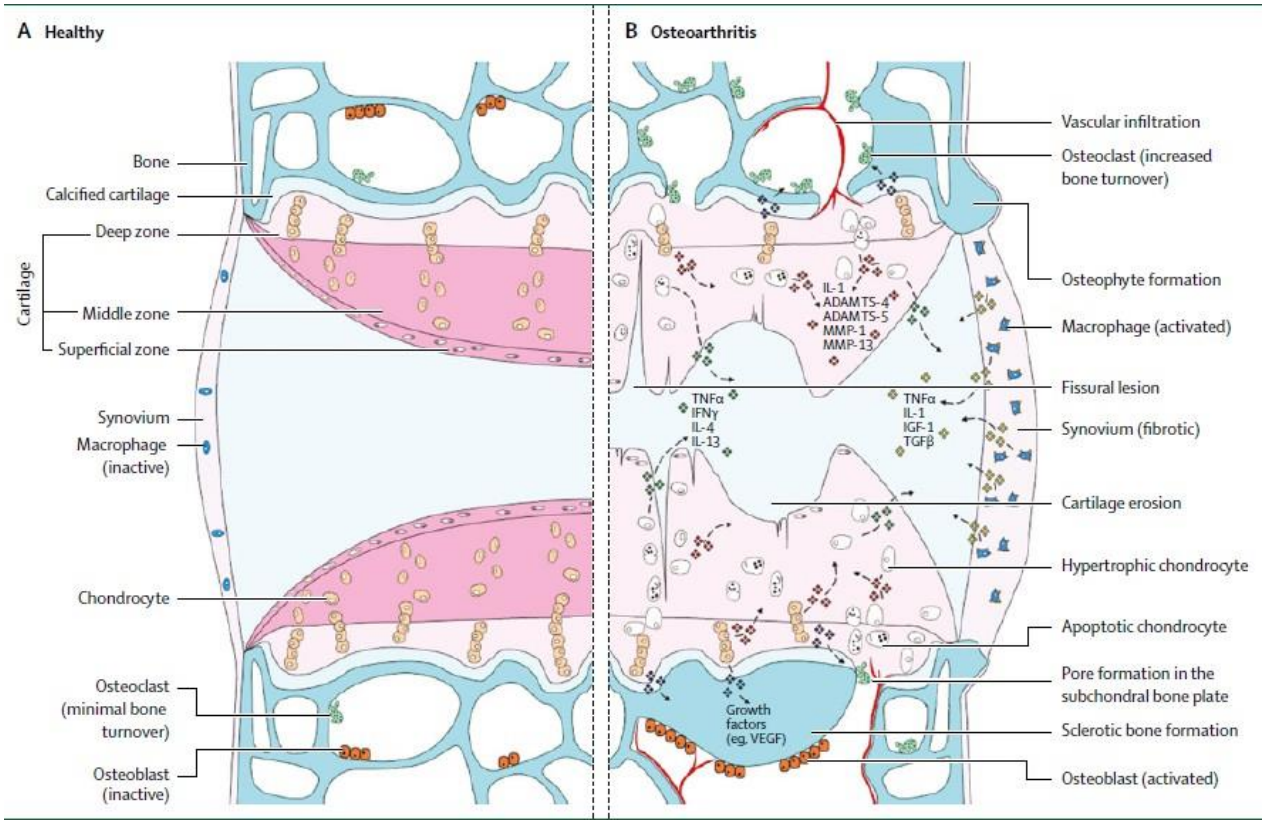


Figure1: Development of osteoarthritis: Signaling routes and changes to structures [33]

2.2. Knee OA:

Knee OA has received greater attention than other joints in terms of prevalence and incidence.[28,34-40] Studies have shown varying levels of the prevalence of symptomatic knee OA. For instance, the prevalence of symptomatic knee OA was 7% among persons aged 45 and older in the US-based Framingham cohort and 17% in the US-based Johnston County Osteoarthritis Project.[39,40] According to a recent meta-analysis, the prevalence of symptomatic knee OA in China was estimated to be 14.6% overall.[41] The National Health Interview Survey reports 14 million US OA-symptomatic knees.[42] 35.1% of 50-year-old Koreans had radiographic knee OA, according to NHANES data.[43] Estimating the frequency of patellofemoral OA especially has garnered attention as well. Around half of those with knee discomfort or radiographic knee OA had patellofemoral involvement, according to a meta-analysis of 85 studies.[44]

According to The Chingford Study, 17.6% of women aged 45 to 64 had radiographic knee OA during a five-year period.[45] Using various cohorts and techniques, it has been shown that the lifetime risk of developing symptomatic knee OA ranges from 14% to 45%.[46,47] Another noteworthy study indicated that the age and sex-standardized incidence rate of symptomatic knee OA among community health plan members was 240 per 100,000 person years, rising considerably after age 50.[48]

2.2.1. Risk factors:

Many studies have shown that the risk of OA rises with aging and is higher in women than in males.[34,35] Except for cervical spine OA, gender differences in OA seem to exist across all joint locations.[34] Differences in race and ethnicity are also widely established. Research from several countries have shown that those with lower socioeconomic positions and those living in rural areas are more likely to get OA, especially at the knee and hip.[49]

It is challenging to predict how many risk factors for illness incidence and progression can change. The distinction between the onset and development of a disease is still up for debate.[50] Index event bias makes it difficult to identify actual progression risk variables, because progression risk depends on both the population examined and the OA definition that is being utilized.[20]

(1) Obesity and metabolic factors: The relationship between obesity and the metabolic syndrome and OA has remained a key area of study.[51,52] One comprehensive analysis indicated that obesity about tripled the risk of OA.[53] Overweight is clearly linked to an increased risk for OA, especially at the knee.[34,35] A comprehensive analysis found no link between metabolic syndrome and hip OA, hand OA, or knee OA in weight-adjusted studies.[54] A recent study found that the metabolic syndrome and low HDL levels were linked to medial compartment cartilage volume loss and an increase in bone marrow lesions, even after controlling for body mass index. However, some metabolic syndrome components were not linked to these changes, and lateral compartment OA was not associated.[55] Moreover, there is some evidence linking specific metabolic syndrome features to worsening knee discomfort.[56,57] Inflammation is one possible mechanism connecting the effects of obesity and metabolic syndrome with those of OA. Nevertheless, the findings have been inconsistent, with one research showing no correlation between interleukin-8 and non-weight-bearing pain. Numerous recent studies have revealed relationships of inflammatory variables with specific features of knee OA severity and symptoms.[58,59]

(2) Physical activity: There has been a false belief that exercise may be bad for weight-bearing joints. More and more research points to the value of physical activity, especially joint loading, in the growth and maintenance of healthy knee joints. Compared to more sedentary kids, physically active kids build up higher cartilage volume.[60] Those who are forced to remain immobile quickly lose cartilage volume.[61]

Yet, there is inconsistent information about whether physical exercise is beneficial or harmful for joints in community-based individuals. These contradictory outcomes might be due to the

joint's underlying health.[62] For instance, in patients with established OA, high levels of physical activity were linked to an increased risk for knee, but not hip, joint replacement surgery; conversely, in healthy people, high levels of physical activity were linked to a protective impact on knee articular cartilage.[63] Joints with structural issues may not be able to support the stresses put on them by physical activity. Heavy occupational and recreational exercise exposure delayed cartilage loss in high-volume people but accelerated it in low-volume persons.[64] Similar to this, increasing daily step count stopped cartilage volume loss in high-baseline cartilage volume people but accelerated it in low-baseline volume persons.[65] Vigorous activity on a knee with bone marrow lesions increased medial cartilage abnormalities and medial tibial cartilage volume loss.[66]

(3) Bone density: Several studies have associated increased bone mineral density to radiographic knee and hip OA.[34,35] A UK Biobank research related high femoral neck bone mineral density to all OA, knee OA, and hip OA.[67] This study's techniques strongly suggest collider bias does not explain the connection between bone mineral density and OA risk.[68] Another study linked bone mineral density to hip and knee replacements.[69] Despite the majority of studies not linking high bone mineral density to OA progression, a recent study found that high bone mass was associated with osteophyte progression when incidence and progression outcomes were combined.[68]

(4) Structural factors: Cartilage Degradation: One of the main characteristics of knee OA is the degeneration of articular cartilage. Collagen and proteoglycans are lost during this process, which makes cartilage less resilient and more prone to injury. A major treatment problem arises because the collagen network cannot be restored to its previous state after it has been destroyed.[70]

Subchondral Bone Changes: The advancement of OA is linked to changes in the subchondral bone, such as bone marrow lesions and accelerated bone turnover. These alterations may worsen the deterioration of cartilage and increase discomfort.[70]

Meniscal Damage: The distribution of stress inside the knee joint is greatly influenced by the menisci. Increased cartilage stress, changed joint mechanics, and the eventual development of OA may result from damage or degeneration of the menisci.[70]

Joint Malalignment: Uneven load distribution across the knee joint is the consequence of malalignment, such as varus or valgus abnormalities. This unequal loading is a major risk factor for the advancement of OA and speeds up cartilage deterioration.[71]

(5) Surgery and injury: Significant risk factors for OA include previous surgery and

significant joint damage. The knee has the most evidence of post-traumatic OA. According to an updated systematic review and meta-analysis, the odds of developing knee OA were 4.2 times higher following an isolated anterior cruciate ligament (ACL) injury, 6.3 times higher following an isolated meniscus injury, and 6.4 times higher for those following a combined ACL and meniscus injury.[72] There is mounting evidence that, in addition to the tibiofemoral joint, the patellofemoral joint is also at higher risk for developing post-traumatic OA.[73,74] A recent knee injury in elderly persons increases their likelihood of developing knee OA more quickly.[74] Nevertheless, there is compelling evidence that a history of knee injury is not related to the advancement of OA as shown on radiographs.[75] In other joints where idiopathic OA is uncommon, including the elbow or ankle, the cause of OA is often a history of joint damage.[76,77] To better comprehend post-traumatic osteoarthritis (OA) in other joints, further high-quality research is necessary. Surgery and knee OA risk are inconsistent. In instance, observational cohorts suggest that arthroscopic meniscectomy is a risk factor for incident radiographic knee OA and OA development in persons without knee trauma.[78]

(6) Other factors: Smoking may have a slight protective impact on the onset of radiographic knee and hip OA, according to certain studies, though results have not always been consistent.[79,80] Statin usage has also been linked to OA in studies, however neither the incidence nor the development of OA was shown to be significantly correlated with statin use in a recent meta-analysis.[81] Nonetheless, there have been some encouraging findings indicating metformin's ability to lower OA risk and development.[82] A recent review of data from the Osteoarthritis Initiative demonstrated a connection between greater diastolic blood pressure and more accelerated degenerative changes in the cartilage matrix over time.[83] Several research have linked blood pressure to OA. Yet, some studies have not shown a connection between OA and blood pressure.[52] There is evidence that hip and knee OA and low birth weight are related.[35] Research has looked at links between different environmental toxins and OA, with lead and organic pollutants such polychlorinated biphenyls showing possible positive connections.[84,85]

2.2.2. Diagnosis and investigation of OA:

(1) Symptoms: Patients with OA often experience pain as their primary symptom. According to a research by Hawker et al., people with OA often report two types of pain: sometimes acute pain and a continuous, nagging background ache.[86] OA pain is known to gradually and sneakily worsen over time. Early on in the course, certain actions lead to the discomfort, which is predicted.[86] Daily activities start to be impacted as time goes on as pain and other joint problems become less predictable and more persistent. In later stages, severe, unexpected

pain is accompanied by ongoing dull, agonizing discomfort, which makes it difficult to engage in certain activities.[87]

Keep in mind that the severity of OA symptoms may not necessarily match the degree of structural disease detected by imaging or the amount of discomfort experienced by the patient. Some people with severe pain have few findings, and vice versa. Prior pain, treatment expectations, psychological difficulties, and sociocultural background might affect how a person feels pain.[88]

Joint swelling, crepitus, clicking, grating, locking, cramping, deformity, and a decreased range of motion are among other non-pain signs of OA. Patients with OA complain of stiffness in the morning, which subsides after 30 minutes. In contrast, rheumatoid arthritis usually lasts a lot longer. Along with increasing activity levels during the day, OA pain also becomes worse. Systemic symptoms ought not to exist. This covers fever, weight loss, and abnormal blood tests. Such symptoms would inform the clinician of additional disease processes, such as cancer or infection.[86]

It has been shown that OA symptoms cause a loss of independence and decrease people's ability to engage in their favorite hobbies.[87] Fautrel et al. conducted a research with 10,000 patients and discovered that 81.5% of those with OA had restrictions in their daily activities, 61.1% reported reduced mobility outside the house, and 12.8% indicated difficulties within the home.[89] Sports and gardening were among the leisure activities that were adversely impacted. In comparison to the control group, those with OA also missed more work. Overall, OA has a major impact on various areas of quality of life (QOL). Although there is undoubtedly a worse quality of life in terms of physical functioning, negative consequences on mental health have also been identified.[89]

(2) Examination findings: Synovial fluid accumulation, joint inflammation, and bone deformities may produce several OA symptoms. Clinical signs include joint line pain, reduced passive and active range of motion, crepitus, joint effusion, bone hypertrophy, and deformity. Polyarticular or single-joint observations are possible. Heberden and Bouchard nodes are also mentioned.[25,86]

Popliteal cysts are often a complication of OA of the knee. Also possible are valgus or varus deformities. On examination, it's usual to find the hip with restricted internal rotation. On physical examination of the shoulder, crepitus and a reduction in range of motion, particularly external rotation, are often seen.

(3) Imaging: OA is generally diagnosed clinically. Plain radiography, however, may be useful in validating the diagnosis and excluding further disease. Rarely are computed tomography and MRI required.[90] Plain radiography signs that are indicative of OA may be seen. Osteoarthritis (OA) often exhibits cysts, osteophyte development, subchondral sclerosis, and joint space constriction.[90]

Extended knee radiographs are utilized to evaluate the knee joint while the patient is weight bearing. Additionally, flexed knee radiographs improve intraarticular visibility. Many grading schemes assess osteophyte production or joint space narrowing. One of the most used OA grading systems is Kellgren-Lawrence.[91]

According to Kellgren and Lawrence, radiographic evidence of OA includes osteophytes on joint margins or tibial spines, periarticular ossicles, narrowing of joint cartilage due to subchondral bone sclerosis, small pseudocystic areas with sclerotic walls in the subchondral bone, and altered bone ends, particularly in the head of the femur.[86,92]

In recent years, new imaging techniques including optical coherence tomography, MRI, and ultrasound have improved the diagnosis and treatment of OA. Articular cartilage degeneration is an indication of advanced OA.[93] Early chondral injury cannot be seen on plain radiographs. Instead, MRI may provide details regarding the dimensions and structural soundness of cartilage. This may be very helpful in detecting changes in the whole or partial thickness of the articular cartilage in OA. Additionally, OA risk factors such as meniscal and anterior cruciate ligament injuries may be found using MRI.[94,95]

Ultrasound detects synovial inflammation and hypertrophy. The Rheumatoid Arthritis Clinical Trials Ultrasonography Taskforce defines ultrasound-detected synovial hypertrophy as hypoechoic, non-displaceable, weakly compressible, and perhaps Doppler-signaled intraarticular tissue.[96] Many benefits come with ultrasound technology, such as cheap cost, no ionizing radiation, the capacity to dynamically scan structures, and the ability to do interventional operations. In deeper joints, such as the hip and shoulder, where ultrasonography is unable to identify OA, MRI may be employed.[96]

(4) Laboratory findings: Laboratory tests in OA patients are usually normal, however they might assist narrow the diagnostic list. C-reactive protein and erythrocyte sedimentation rate may detect autoimmune and systemic inflammatory disorders. Uric acid level might be used to test for gout. The American College of Rheumatology's clinical recommendations advise against routinely conducting arthritis panels for individuals with joint issues.[97]

2.2.3. Treatment:

(1) Pharmacologic treatment: ACR guidelines recommend treating arthritis with topical cream, NSAIDs, steroidal drugs, and integrative therapy. Cream containing capsaicin may help with joint discomfort. Chili peppers contain capsaicin, which may warm and desensitize neurons as a result of P selectin deletion.[98] In senior diabetic people, it may raise their chance of developing skin ulcers.[99] The two cornerstones of arthritis treatment are NSAIDs and acetaminophen. COX-2 inhibitors are the second line of therapy for this category of medications. All of these medications have adverse effects that restrict their use. The dose and length of therapy are increased by unfavorable hepatic, gastrointestinal, and cardiorenal consequences. A steroid-like corticosteroid injection into the joint reduces inflammation.[100] Although they may lessen pain and illness symptoms, their use is restricted by adverse effects.[101] Another method that has expanded the therapy options for OA is the use of nanoparticles with controlled size for intra-articular injection. The benefits of nanoparticles include biodegradability, high stability, inclusion of hydrophilic and hydrophobic compounds, and various delivery methods. Drugs may be carried by nanoparticles on their surface, protected from enzymatic deterioration, and better absorbed via the cartilage matrix.[102]

Intra-articular injections of hyaluronic acid or its derivatives, known as Visco supplementation, improve joint function following several weeks of treatment, but they might cause side effects and should be customized to each patient.[103]

(2) Non-pharmacologic treatment: The ACR recommends land-based and aquatic activities based on patient comfort and desire as exercise improves function and reduces pain for these patients.[104] Vignon et al. reported a decrease in pain and stiffness.[105] Additionally, some tools like braces, walking canes, and the right footwear can help a patient function more normally. Further harm may be avoided by teaching patients' energy-saving and joint-protection strategies. TENS and pulsed electromagnetic field stimulation devices are alternative non-pharmacologic options. These methods' effects on OA have been extensively studied. These approaches deal with acute and chronic pain.[106] Another technique for reducing pain in these people is acupuncture therapy, particularly when used in conjunction with pharmacological treatment alternatives. Other treatments include magnetotherapy, balneotherapy, glucosamine sulfate, and glycosaminoglycans, some of which have demonstrated only modest benefits.[106-109] In addition to the approaches already described, certain suggestions may be helpful for these patients, including aerobic workouts on the ground, lifestyle changes like weight loss for patients who are overweight, psychological therapies, and self-management programs.[110]

(3) Surgical treatment: Surgical intervention is the final option for OA patients. Various procedures are used during surgical therapy. Chondral lesions are found during the arthroscopic process.[111] This technique may be used to remove loose pieces of the lesion, but it merely relieves patients' discomfort; it does nothing to stop the progression of OA, and any residual cartilage would be vulnerable to deterioration.[112,113] Microfracture penetrates subchondral bone and allows bone marrow to fill the injury. Bexkens et al. found 60% of patients improved and resumed activities.[114] Another interventional treatment is mosaicplasty, or osteochondral autologous transplantation, in which osteochondral plugs are removed from a healthy location and transplanted to the damaged area.[115] Poor integrity, Site morbidity, and long-term deterioration are drawbacks and consequences of this approach. Young people with OA that is isolated to one compartment have osteotomies, however complete arthroplasty is a possibility for older patients with progressive OA.[112]

2.3. Osteopontin

2.3.1. Intro to osteopontin: Osteopontin (OPN), a multifunctional phosphoprotein with 44–75 KD, is released by a number of different cell types, including chondrocytes, osteoclasts, synoviocytes, lymphocytes, macrophages, epithelial cells, and vascular smooth muscle cells (SMC). Furthermore, it may be discovered in extracellular fluids and the extracellular matrix of tissues that have undergone mineralization at inflammatory sites.[116-118] It is produced by the SPP1 gene, which also produces full-length OPN and spliceosomal OPN.[119,120] SPP1 encodes it and aligns as a tandem array to the long arm of chromosome-4.[121] Thrombin cleaves full-length OPN into thrombin-cleaved OPN.[122] Both the native and cleaved forms of OPN have the potential to interact with integrin and have a significant impact on the control of immunological responses, inflammation, bone remodeling, biomineralization, chemotaxis, and cell death.[122,123] Based on gene structure and chromosomal positioning, OPN is a small integrin-binding ligand N-linked glycoprotein (SIBLING). This protein, also known as early T cell activation gene-1 (Eta-1), is broadly distributed in bone and is essential for cell-matrix and cell-cell communication.[124] OPN expression is important in fracture healing during chondrocyte development.[125,126] It helps osteoclasts bind to bone matrix through cell surface αvβ3 integrin and CD44.[127,128] Integrin and CD44 receptors help OPN regulate differentiation, proliferation, metabolism, inflammation, and tumor metastasis in osteoclasts, chondrocytes, and osteoblasts.[129-131] According to research, OPN regulates OA and osteocyte and chondrocyte metabolism through influencing articular cartilage and subchondral bone extracellular matrix components.[132-134]

OPN is a vital intrinsic regulator that is crucial to the development and progression of OA. OPN levels are greater in OA patients' synovial fluid and plasma than they are in healthy people,

which may indicate a relationship between OPN and how severe the disease's joint lesions are.[135] When Min et al. looked at the serum of 249 individuals, they discovered that the concentration of OPN in the OA group was much higher than in the control group, and that there was also a gender difference between the two groups.[136] Compared to OA patients, the control group's blood OPN level was 2539.9 (pg/ml) and 5538.1 (pg/ml) in men and 1632.0 and 4545.8 in females which is low. This was the major way OPN expression differed by gender. Other research found that OPN gene polymorphism reduces OA risk.[137] They found that higher OPN mRNA and protein expression in synovial fluid of OA patients closely correlates with OA development.[138] Recent studies have indicated that OA patients had greater OPN expression in both the superficial and deep articular cartilage.[139,140] In animal research, elevated OPN expression motivates subchondral bone vascular growth, facilitates articular cartilage degradation caused by metabolism, and accelerates OA.[141] It accelerates OA subchondral bone turnover and remodeling. According to some conflicting findings, OPN treats OA. Elevated OPN may delay chondrocyte degeneration and cartilage matrix component loss via binding to CD44 and integrin through the OPN/CD44/PI3K signaling pathway.[142] OA chondrocytes upregulate OPN, CD44, and mRNA. Hyaluronan (HA) and OPN are CD44's main ligands. [143] CD44 variants with exons v6 and v7 bind to OPN's N- and C-terminals in an arginine-glycine-aspartic-independent manner to govern bone metabolism.[144] According to Zhang et al., HA might boost the production of OPN mRNA in synoviocytes that resemble fibroblasts in OA, and the high expression of OPN mRNA in OA may be caused by an increase in HA levels in the synovitis, ultimately reducing the severity and easing the symptoms of OA.[145] The progression of chondrocytes and the severity of OA may be accelerated by OPN deficiency, which may also up-regulate the production of pro-inflammatory molecules and reduce the expression of COL2A1.[130]

2.4. Role of osteopontin in OA

2.4.1. Osteopontin has a role in OA inflammation: OPN is significantly expressed throughout the inflammatory process. The significance of OPN in inflammation activity has been extensively studied, and it is crucial to the pathophysiology of many inflammatory illnesses, including OA.[146] It has been shown that OPN is a key player in the pathophysiology of arthritis and is a pro-inflammatory cytokine. In synovial fluid samples from RA patients, OPN is expressed at a greater level and correlated with high levels of numerous inflammatory cytokines, including IL-6 and TNF-a.[147] Another study confirms OPN protein synthesis in advanced OA synovial fluid. Higher Kellgren-Lawrence scores show significant connections between thrombin-cleaved OPN, synovitis, and cartilage deterioration.[148] A long-term cohort research found that CRP, IL-6, and OPN levels spiked the day after arthroplasty and returned to baseline six weeks later. TNF-a levels did not change preoperatively or postoperatively,

although IL-8 and IL-1b levels peaked at 5 years after surgery and returned to normal levels after 10 years.[149] Total joint arthroplasty patients' blood samples showed increased OPN and MMP-9. IL-1, IL-6, and CRP increase MMP-9, which cleaves OPN to destroy Cola2a1.[7] These Inflammatory biomarkers may cause OA and total joint arthroplasty. OPN levels rose considerably in synovial fluid samples from symptomatic primary knee osteoarthritis patients with ultrasound-confirmed joint effusion. IL-8 and TNF, which cause pain, cartilage destruction, clinical severity, and OA development, were linked to higher OPN levels.[150] Wang et al. observed that OPN may inhibit the production of various inflammatory markers, including MMP-13, IL-6, and IL-8, which were significantly enhanced in OA tissues and associated to the disease's pathogenesis.[151,152] The link between OPN and OA inflammatory variables has also been the focus of several medicines. In MIA-induced rats, isorhamnetin might lessen knee edema and repair cartilage degradation. The therapeutic effect was primarily attained by suppressing the expression of OPN and the type II collagen C-terminal telopeptide (CTX-II), along with a reduction in the levels of iNOS, NO, PGE2, and COX-2.[153] OPN does, however, serve a protective function in OA, according to some contentious findings. Normal chondrocytes have much lower OPN mRNA levels than OA chondrocytes.[130] OPN deficiency increased chondrocyte senescence and death by increasing TNF-, MMP-13, IL-1b, Col10a1, and ADAMTS-5 and lowering Col2a1.[154] OPN depletion stimulated MMP-13, which breaks down type II collagen in instability-induced and aging-associated OA. This shows OPN is critical to OA formation. Thus, OPN may be a biomarker for OA's inflammatory activity as either a high or low OPN level might release inflammatory chemicals, damage articular cartilage, and aggravate OA.[154]

The above findings and research focused on OPN's role in regulating inflammatory activity in OA and suggested that metabolic disruption in bone illnesses may result from increased or decreased OPN expression in chondrocytes and synoviocytes.

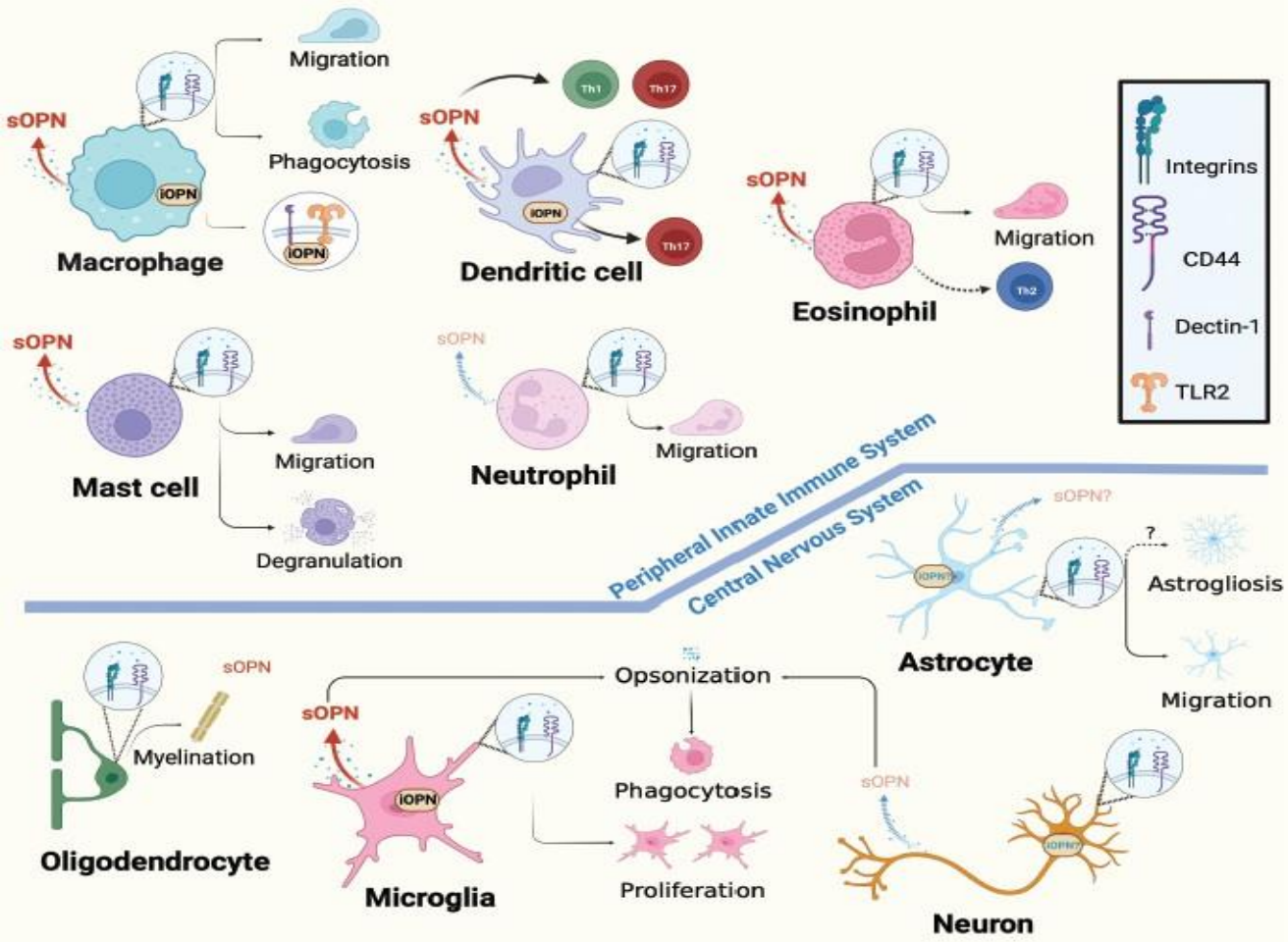


Figure 2: The expression of OPN and its consequences in distinct cell types.[155]

2.4.2. OPN affects the metabolism of bone and cartilage in OA:

Different kinds of cells that are found in several cells and tissues, including macrophages, chondrocytes, lymphocytes, vascular smooth muscle cells, epithelial cells, and synovial cells, release OPN.[156-158] The onset of OA is linked to abnormal OPN mRNA or protein expression.[122,132,156] Upregulated and phosphorylated OPN in chondrocytes and synovial fluid worsen OA.[158] Overexpression of OPN may increase chondrocyte proliferation and decrease mortality through the NF-kB signaling pathway to reduce OA degeneration, according to current studies. OPN serum levels are associated with the frequency of tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts and bone deterioration in CIA mice, however lentiviral-OPN short hairpin RNA silences OPN.[159] Elmazoglu et al. found that S-allylcysteine suppressed OPN and bone morphogenetic protein-7 (BMP-7), reduced inflammatory response, and decreased IL-1b, IL-6 in chondrocytes, reducing OA severity.[160] OPN degrades cartilage and remodels subchondral bone in OA.[161]

OPN modulates chondrocyte, synovial cell, and subchondral bone metabolism, which affects joint function, hence it must be carefully regulated to prevent OA.

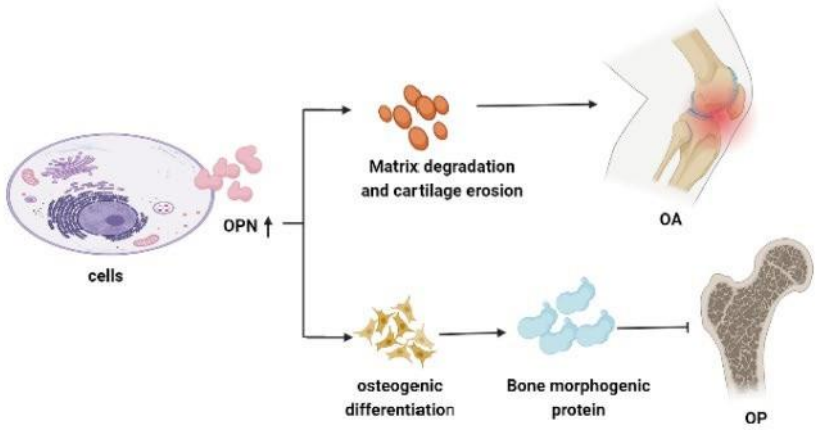


Figure 3: The involvement of OPN in cartilage and bone metabolism in OA and OP.[162]

2.4.3. Pharmacological approaches for OPN in OA:

OPN has a complicated impact, which makes controlling its expression a difficult procedure. Some old and new medications have recently looked into how OPN affects OA. OPN level in chondrocytes, synovial tissue, and synoviocytes have been the major targets of pharmaceutical treatments in OA up to this point.[146] S-allylcysteine was discovered to be able to block IL-1b, IL-6, and OPN in chondrocytes by reducing the activity of the p-JNK/pan-JNK signaling pathway, according to Elmazoglu et al.[160] The upregulation of type-II collagen and peroxidase as a result of the suppression of OPN and these cytokines ultimately helped to slow the progression of OA. Chitosan oligosaccharide-containing extracellular vesicles were examined in OA by Li et al. Chitosan oligosaccharides prevented IL-1b-induced chondrocyte death, viability, and migration. Chitosan oligosaccharides decreased cartilage injury by down-regulating OPN, p53, and IL-1b and up-regulating OCN, Col2a1, and Runx2 through the PI3K-Akt pathway. By regulating the level of OPN in rats, isorhamnetin also greatly lowered the damage to the articular cartilage and, therefore, MIA-induced knee edema.[152] [153]

Isorhamnetin prevented the development of OA by inhibiting OPN, iNOS, NO, COX-2, and PGE2. OPN and MMP-9 levels were shown to be considerably higher in OA, according to Slovacek et al.[7] the heightened levels of OPN and MMP-9 are triggered by inflammatory markers such IL-1, IL-6, and CRP. Previous studies indicated that adiponectin worsens bone erosion by encouraging the synthesis of OPN in synovial tissue, whereas lentiviral-OPN short

hairpin RNA silencing of OPN might lessen the quantity of TRAP-positive osteoclasts and the severity of bone erosion in CIA mice. The expression of OPN in OA may also be influenced by the microRNA (miR). As a treatment for OA, miR-181c might significantly reduce the impact of OPN on inducing MMP-13, IL-8, and IL-6 secretion as well as suppress synoviocyte proliferation. This would ultimately reduce local inflammatory activity and cartilage destruction in joints.[7]

Recently, the focus on OA early diagnosis has increased, and conventional therapy has improved the prognosis, but OA treatment is still inadequate. To create cutting-edge treatment approaches, a deeper comprehension of the pathogenic process of OA is necessary. The proper mediators of joint degeneration must be identified in order to effectively prevent and treat OA.[163] OPN may be a potential biochemical diagnostic for the diagnosis of OA since it is commonly detected at high levels in the plasma and synovial fluid of OA patients.[156,164,165] Abdelnaby et al. recommended OPN as a diagnostic and prognostic tool to assess the severity of OA symptoms in a recent research.[141] In order to detect the condition early, gauge its severity, and provide safe and efficient disease-modifying therapies for OA patients, the use of biochemical markers has been advocated. Consequently, OPN may be a helpful diagnostic biomarker for the diagnosis and management of OA.

The results of this study aim to provide future benefits for patients with knee osteoarthritis, as well as a better medical understanding of the response of osteopontin plasma levels in relation to knee replacement surgery and its immunological correlation.

3. Material and methods

Overview

This study included thirty symptomatic patients with osteoarthritis of knee joint who were scheduled for knee replacement surgery. The plasma levels of OSP (Osteopontin) were measured before the operation and six months after the operation using an enzyme-linked immunosorbent assay (ELISA). By the results of this study, we expect to provide future benefits for patients with the aforementioned condition, as well as a better medical understanding of the response of osteopontin plasma levels in relation to knee replacement surgery and its immunological correlation.

Inclusion criteria:

Consenting patients of both genders aged above 50 years with idiopathic osteoarthritis of the knee joint (Grade 3 and 4 according to the Kellgren Lawrence Score) who were candidates for total knee replacement (TEP) surgery.

Exclusion criteria:

Patients with secondary osteoarthritis, other types of arthritis such as rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, gout, pseudogout, and infectious arthritis. Also, patients with osteoporosis, systemic inflammatory or autoimmune diseases, or malignant diseases were excluded.

The following were performed for all patients:

• **Comprehensive medical history**: Gender, age, occupation, menstrual history, with a particular focus on knee pain, morning stiffness, joint swelling, other joint stiffness, joint diseases.

• **Patient Recruitment:** Patients were recruited from the orthopedic clinic of Mühlenkreiskliniken in Lübbecke. The research has received approval from the appropriate Research Ethics Committee in Cologne University, and the participants signed a permission form confirming to its adherence to the highest ethical standards and protection of their rights, safety, and well-being.

• **Detailed clinical examination:** Weight and height (BMI calculated). Local examination of the knee joint for tenderness, warmth, swelling, effusion, crepitus, palpable osteophytes, deformities, synovial hypertrophy, range of motion, muscle atrophy, ligament laxity, and patella femur compression test. Also, examination of small joints of hands and feet, shoulders, hip

joints, and ankle joints as screening for primary generalized osteoarthritis and gait examination.

• **Laboratory investigations:** Routine laboratory investigations using a total cell count, serum CRP (C-reactive protein) using an enzyme-linked immunosorbent assay (ELISA) were carried out at Laborkrone in Bad Salzuflen.
Measurement of OPN (Osteopontin) levels in plasma samples: Blood samples were taken from all patients, centrifuged, and stored at ≤ -20 °C until analysis. The double-blind quantitative detection of osteopontin levels in plasma was performed using an enzyme-linked immunosorbent assay (ELISA).

• **Knee radiography:** Standardized X-rays of the knee with anteroposterior stress were performed and evaluated according to the severity scale of Kellgren and Lawrence (K/L) for knee OA (Kellgren and Lawrence, 1957), where Grade 0 = normal; Grade I = doubtful joint space narrowing and possible osteophytic lip formation; Grade II = definite osteophytes and possible joint space narrowing; Grade III = moderate multiple osteophytes, clear joint space narrowing, some sclerosis, and possible bone contour deformity; and Grade IV = large osteophytes, severe joint space narrowing, severe sclerosis, and definite bone contour deformity.

• **Data Privacy:** To protect the privacy of study participants, the data was anonymized. All patients provided a general consent form regarding the use of medical data upon admission. The participant's data was then deleted. The physicians and technical assistants involved in the study are bound by confidentiality.

Statistical analysis: All analyses were performed with IBM SPSS version 25 software for Windows. Descriptive statistics are performed for sociodemographic characteristics. Normal test was conducted. Wilcoxon Signed Ranks test was used to compare OPN level between pre and post operative. A P value .05 was considered to indicate statistical significance.
Dr. Ramy Abdelnaby, a colleague from the Department of Neurology at Aachen University, skilled in statistics and handled the statistical analysis for my study.

4. Results

A total of 30 patients were enrolled in our study, 12 of them are male, mean age of the population is 71.5 years with BMI of 29.9 as shown in Table 1.

Table 1: Population characteristics.

Variable	N (%)
Gender	
Male	12(40)
Female	18(60)
BMI	29.97(5.3) *
Age (Y)	71.5(18) **
ASA	
1	1(3.3)
2	19(63.3)
3	10(33.3)

*Mean and SD **Median and interquartile range

Concerning comorbidities and risk factors of the patients, 19 of them are hypertensive, 10 have hypothyroidism, and 6 are smokers. Other comorbidities are shown in Table 2.

Table 2: Comorbidities and risk factors associated with the patients:

Comorbidities	N (%)
DM	3(10)
Hypertension	19(63.3)
Smoking	6(20)
Renal failure	1(3.3)
Arrhythmia	2(6.7)
Coronary heart disease	2(6.7)
Stroke	1(3.3)
Thrombus	4(13.3)
Pulmonary embolism	1(3.3)
Hypothyroidism	10(33.3)
COPD	4(13.3)
Depression/psychosis	0
Blood transfusion	2(6.7)

Alcohol abuse	1(3.3)

Pre-Operative evaluation of plasma OPN level among knee surgery patients ranged from 14.3 ng/ml to 241.2 ng/ml with a mean level of 73.4 ng/ml meanwhile, 6 months post operative mean level increased to 84.9 ng/ml. Table 3.

Table 3: Pre and 6 months post operation OPN of the patients:

	Preoperative		6 months post operative	
Labs	Mean (SD)	Range	Mean (SD)	Range
OPN (ng/ml)	73.4(45.1)	14.3-241.2	84.9(42.5)	18.4-176.05

OPN: Osteopontin , SD: standard deviation

A Comparison between levels of OPN in knee surgery patients (pre-operatively) and normal values was done and revealed a high statistically significant difference p value 0.0002. Table 4.

Table 4: Comparison between levels of OPN in knee surgery patients (pre-operatively) and normal values revealed a high statistically significant difference.

Variable	Preoperative Mean (SD)	Normal reference Mean (SD)	P value
Plasma OPN (ng/ml)	73.4(45.1)	94.8(24.9)	0.0002*

*Statistically significant

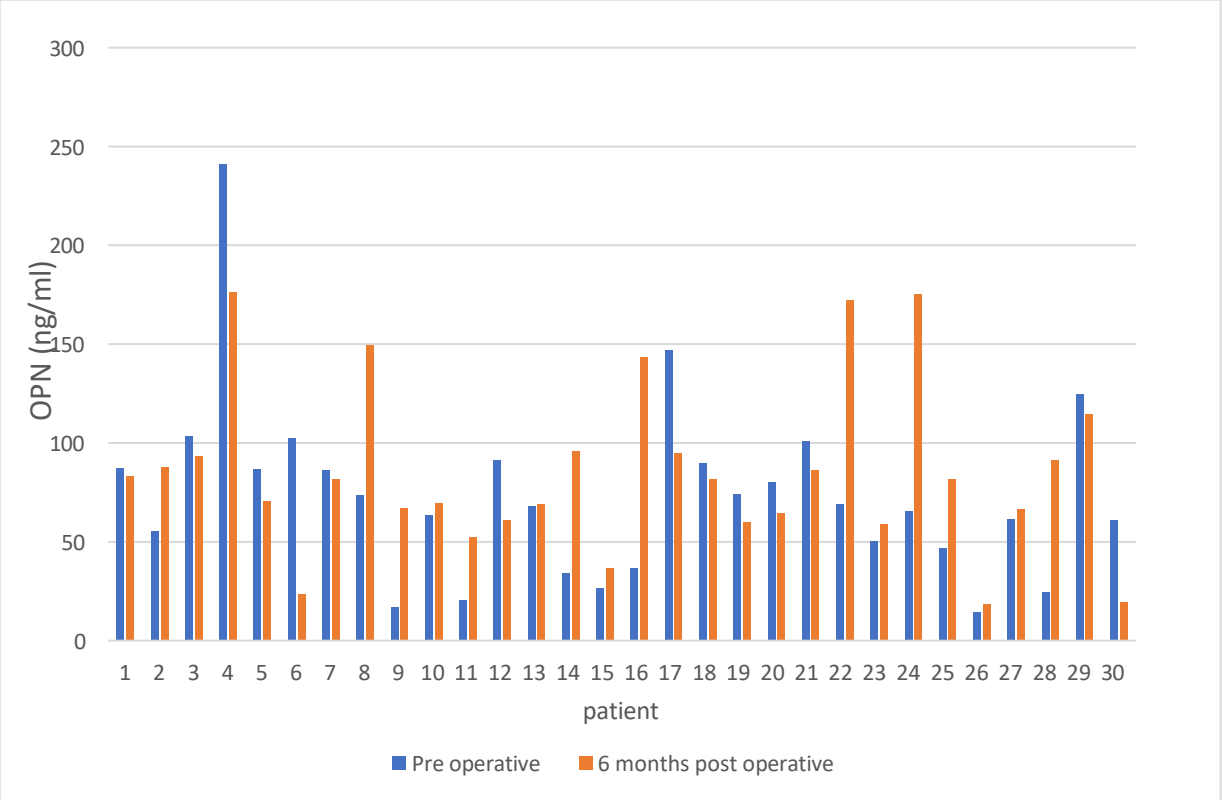
Pre and post operative evaluation of CRP is done to exclude post operative infection to meet our criteria.
It ranged from 0.6 (µg/ml) to 12 (µg/ml) with a mean level of 1.6 (µg/ml) whereas post operative mean was 35(µg/ml) Table 5.

Table 5: Pre and post operative CRP of the patients:

	Preoperative		Post operative	
Labs	Mean (SD)	Range	Mean (SD)	Range
CRP (µg/ml)	1.6(2.23)	0.6-12	35(33)	0.7-99.4

CRP: C reactive protein, SD: standard deviation

Figure 4: Pre and post operative OPN value:



We conducted Wilcoxon Signed Ranks test to study difference in OPN between pre and post operative, results showed that there is no statistically significant difference in OPN between pre and post operative Table 6.

Table 6: Wilcoxon Signed Ranks test to identify the difference in OPN between pre and post operative in knee surgery:

Variable	Z	P value
Plasma OPN	-0.7	0.465

5. Discussion

The presence of Osteopontin (OPN) in plasma and synovial fluid of patients suffering from rheumatoid arthritis and osteoarthritis has been reported before. [166] OPN itself is an O-glycosylated phosphoprotein that is produced in different cells and tissues and secreted in our bodies. Recently, OPN has been getting deserved attention in biomedical research and tissue repair mechanisms, especially due to its diverse functions. It can interact with numerous universally expressed receptors. This underscores its crucial role as an active participant in numerous physiological and pathological processes, such as wound healing, bone remodeling, tumor development, inflammation, ischemia, and immune responses. [167] A critical portion of OPN's role is its ability to modulate immune responses at different levels. For example, it has chemotactic properties that allow cell recruitment to the sites of inflammation. Moreover, it acts as an adhesion protein that facilitates cell attachment and, subsequently, contributes majorly to wound healing. Additionally, OPN's modulation of cytokine production through interaction with cellular signaling pathways remains an important pathway for immune modulation. Upregulation of OPN can therefore lead to activation of cytokine production such as interleukin-1 beta (IL1B), tumor necrosis factor (TNF), chemokine (C-C motif) ligand 2 (ccl2), and chemokine (C-X-C motif) ligand (cxcl) which are involved in the intensification and spread of inflammatory responses. [167] OPN's activation of cytokine production contributes to immune response and coordination of inflammation. OPN-stimulated pro-inflammatory mediators produced in the synovial membrane diffuse into the synovial fluid and to cartilage leading to the activation of chondrocytes and, consequently, the production of catabolic factors such as proteases leading to further cartilage damage. [168] The versatile role of OPN in immune modulation and tissue repair has made it the center of attention of researchers in the field of osteoarthritis. By definition, osteoarthritis is a disorder characterized by cartilage breakdown and inflammation. [169] By understanding the role of OPN in the pathogenesis of osteoarthritis and whether it can be considered a biomarker for disease progression and treatment response is vital for researchers and clinicians alike.

5.1. Plasma level of OPN as a biomarker for follow-up

Ours revealed that plasma OPN increased after six months of total knee replacement surgery in 30 patients suffering from osteoarthritis (mean OPN after=84.9 ± 42.5 ng/ml Vs. mean OPN before 73.4 ± 45.1 ng/ml). A Wilcoxon Signed Ranks test was performed to evaluate the difference between pre-and post-operative plasma OPN, and it showed a Z-value of -0.7 and a p-value of 0.465. This means that, even though our results show an increase in plasma OPN

post-total knee replacement surgery, this difference is statistically insignificant meaning that there is a 46.5% of observing a difference as extreme as the one obtained in our sample due to random chance alone, assuming there is no true difference between pre-and post-operative OPN levels. Biological responses following surgery can be complex and multifaceted. The absence of a statistically significant decrease in plasma OPN levels after surgery may be attributed to the surgical intervention itself which can trigger inflammation and tissue healing processes which, by itself, may lead to an increase in certain biomarkers including OPN. Indeed, this hypothesis can be explained by the observed rise in CRP post-operatively compared to pre-operatively (mean CRP after = 35±33 µg/ml Vs. mean CRP before = 1.6±2.23 µg/ml). Additionally, the release of OPN could be influenced by other factors such as the severity of osteoarthritis, individual patient variability, and the specific surgical techniques employed. Similarly, Abdelnaby et al. [170] examined the OPN levels pre-and post-knee replacement surgery in 16 patients suffering from osteoarthritis. The researchers discovered that osteopontin did not show a significant decrease three months after the surgery. Instead, it exhibited a notable increase following the surgery (p=0.001). However, the levels of plasma OPN they measured before and after the surgery were higher than the ones we obtained (average OPN before = 305.55 ± 55.97 ng/ml, average OPN after = 434.2 ± 144.85 ng/ml). They attributed the observed rise in OPN levels three months after knee surgery to its release from the bone, cartilage, or synovium during the operation. This finding supports our hypothesis and aligns with previous studies that suggest OPN serves as an early response marker to stress signals.[171,172] The difference between plasma OPN levels in our patients and Abdelnaby's may be attributed to several factors such as included patients' characteristics, disease severity, surgical techniques, and sample size. Another cross-sectional study by García-Manrique et al.[173] reported lower blood OPN levels in 115 women with symptomatic primary knee osteoarthritis than our study (median OPN= 10.97 ng/ml). However, Abdelnaby et al.[174] published a systematic review in 2023 of Web of Science, Scopus, PubMed, and Embase and meta-analyzed patients' data from fourteen studies assessing whether OPN has the potential to serve as a diagnostic or prognostic marker for the severity of osteoarthritis symptoms. Three studies [175-177] assessed the serum OPN levels in osteoarthritis patients versus controls. Compared to control group, OPN levels were statistically higher in the osteoarthritis group (SMD=3.83, 95% CI=0.23,7.43). Indicating its potential as a diagnostic and prognostic marker to determine the severity of osteoarthritis symptoms. However, heterogeneity was statistically significant among meta-analyzed studies (I2 = 99%, P < 0.00001) due to variations in OPN measurement kits used and their different calibration levels. Nevertheless, only Dong et al. [176] had statistically insignificant results (SMD=0.12; 95%CI=-0.48, 0.71). While this study suggests that we can use plasma OPN as a diagnostic and prognostic parameter for determination of severity of osteoarthritis, our results may suggest

otherwise. However, our results may be confounded by surgical techniques, patient variations, or single relatively short period of follow-up.

5.2. Limitations

The present study has some limitations. For instance, our study had a relatively small sample size of 30 patients, which may restrict the generalizability of our results. By including a larger and more diverse sample, we would be able to obtain a more comprehensive understanding of the association between plasma OPN levels and knee replacement surgery in patients with osteoarthritis. Moreover, the absence of control group makes it difficult to determine if the observed OPN levels are solely attributable to knee surgery. We suggest future researchers include a control group of osteoarthritis patients who do not undergo surgery to help establish a baseline for comparison. Lastly, we only measured OPN levels at a single time point, six months after knee replacement surgery. We may obtain a more comprehensive understanding of dynamic changes in OPN levels over time if we monitored OPN levels at multiple points pre- and post-surgery.

5.3. Recommendations:

We suggest that future researchers pursue longitudinal studies with larger sample sizes to allow for assessment of plasma OPN levels at multiple time points before and after surgery. This would allow us to identify trends or patterns in OPN changes and determine its role as a potential biomarker for disease progression and treatment response. Moreover, as mentioned earlies, future researchers should focus on including control groups such as non-surgical osteoarthritis patients or individuals undergoing different surgical procedures to compare OPN levels and determine the specific impact of knee replacement surgery on OPN levels. This may, however, be challenging because of the ethical considerations of subjecting a group of patients with osteoarthritis, who may require surgery for pain relief or functional improvement, to a non-surgical treatment. It may not be feasible or ethical to withhold surgical intervention from patients with significant disease burden. Lastly, future researchers should pursue mechanistic studies to investigate the underlying mechanisms by which knee surgery impact OPN levels in osteoarthritis patients. This includes examining the interaction between OPN and inflammatory cytokines, the specific cellular sources of OPN release, and the role of other factors such as severity of the disease and surgical techniques.

5.4. Conclusion:

The present study examined the plasma OPN levels before and after six months of total knee replacement surgery in 30 osteoarthritis patients. While an increase in OPN levels was observed, it was statistically insignificant suggesting that the OPN cannot be a detector for OA in the knee and also that surgical intervention may trigger complex biological responses that influence OPN levels.

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7. Appendices

7.1. List of Figures

7.2. List of tables