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Die Reaktion der Osteopontin-Werte im Plasma vor und nach Implantation einer Total-En-doprothese des Hüftgelenks bei Patienten mit schwerer idiopathischer Osteoathrose

(The Response of Plasma Level of Osteopontin to Total Replacement Surgery in Patients with Severe Primary Hip Osteoarthritis)

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List of Abbreviations

(ACR)	American College of Rheumatology
(BMI)	Body Mass Index
(CCL2)	C-C motiv chemokine ligand 2
(CI)	Confidence Interval
(CIA)	Collagen-Induced Arthritis
(COL2A1)	Collagen Type II Alpha 1 Chain
(COX-2)	Cyclooxygenase-2
(CRP)	C-Reactive Protein
(CXCL)	C-X-C motiv chemokine ligand
(DC)	Dendritic Cells
(ECM)	Extracellular matrix
(ELISA)	Enzyme-Linked Immunosorbent Assay
(Eta-1)	Early T cell activation gene-1
(GBD)	Global Burden of Diseases
(HOA)	Hip osteoarthritis
(ICAM1)	Intercellular adhesion molecule 1
(IL1)	Interleukin 1
(IL1B)	Interleukin 1B
(IL6)	Interleukin 6
(IL8)	Interleukin 8
(IL12)	Interleukin 12
(iNOS)	Inducible nitric oxide synthase
(JSW)	Joint Space Width
(LDL)	Low-density lipoprotein

(LPS)	Lipopolysaccharide
(MetS)	Metabolic syndrome
(MHC)	Major Histocompatibility Complex
(MIA)	Mono sodium iodoacetate
(miR)	microRNA
(MJOA)	Multiple-joint Osteoarthritis
(MMP-13)	matrix metalloproteinase-13
(MMP-9)	matrix metalloproteinase-9
(MRI)	Magnetic Resonance Imaging
(mRNA)	Messenger ribonucleotides
(NF-κB)	Nuclear factor kappa B
(NK)	Natural Killer
(NO)	Nitric Oxide
(NSAIDs)	Nonsteroidal Anti-Inflammatory Medications
(OA)	Osteoarthritis
(OCN)	Osteocalcin
(OPN)	Osteopontin
(PGE2)	Prostaglandin E2
(PI3K)	Phosphoinositide-3-kinase
(ROS)	Reactive Oxygen Species
(RUNX2)	RUNX Family Transcription Factor 2
(SD)	Standard Deviation
(SIBLING)	Small integrin-binding ligand N-linked glycoproteins
(SMD)	Standard Mean Difference
(SPP1)	Secreted phosphoprotein 1

(TH1)	T cell helper 1
(THRs)	Total Hip Replacement
(TKRs)	Total Knee Replacement
(TNF-a)	Tumor Necrosis Factor-alpha
(TRAP)	Tartrate-Resistant Acid Phosphatase

1. Summary

1.1. Summary

This study measured plasma level of osteopontin in 30 patients with severe idiopathic hip joint arthritis, before and six months after they underwent total hip replacement surgery. The results of this study aim to demonstrate the correlation between pre- and postoperative plasma osteopontin levels and determine whether it is possible to predict the outcome of total hip replacement surgery for individual patients based on these values. Furthermore, the study aims to enhance understanding of the immunological function of plasma osteopontin. Although a decrease in osteopontin levels was noted six months after surgery, the reduction was not statistically significant. To enhance the applicability of future research, we recommend increasing the sample size to improve statistical power. Furthermore, longitudinal studies with extended follow-up periods are encouraged to gain a more comprehensive understanding of the changes in plasma osteopontin levels after surgery.

1.2. Abstract

Introduction: Hip osteoarthritis (OA), which affects 8% of the world's population overall, is a significant contributor to hip discomfort, functional impairment, and a poor quality of life. Throughout the inflammatory process, Osteopontin (OPN) is strongly expressed. Numerous studies have been done on the importance of OPN in inflammation activity, and it is essential to the pathophysiology of many inflammatory diseases, including OA. **Method:** The investigation entailed measuring the plasma osteopontin levels pre- and postoperatively in 30 patients with severe idiopathic hip joint arthritis who were candidates for complete hip replacement surgery. Patients' osteopontin levels were assessed before and six months after surgery.
Results: Our research included 30 patients in all, 16 of them were men. The mean age is 74.3 years. The pre-operative plasma OPN levels varied from 12 ng/ml to 167.2 ng/ml, with a mean level of 87.4 ng/ml. Meanwhile, the 6 month post-operative mean level has dropped to 78.5 ng/ml (Range 10.9 to 165.4 ng/ml). **Conclusion:** Despite the fact that we observed a drop in OPN levels compared to before surgery at 6 months, the difference was not statistically significant. This implies that the observed drop in plasma OPN levels after surgery may be due to random variation or other aspects of the operation.

Key Words: Osteopontin, Osteoarthritis, Hip.

1.3. Summary in the German Language (Zusammenfassung)

Im Rahmen dieser Studie wurde die Plasma-Osteopontin-Spiegel bei 30 Patienten mit schwerer idiopathischer Hüftarthrose vor und sechs Monate nach einer Hüft-TEP (Total-Endprothese) Operation gemessen. Die Ergebnisse dieser Studie zielen darauf ab, die Korrelation zwischen prä- und postoperativen Plasma-Osteopontin-Spiegeln zu demonstrieren und zu bestimmen, ob es möglich ist, die Prognose und den Nutzen der Hüft-TEP Operation für einzelne Patienten basierend auf diesen Werten vorherzusagen. Darüber hinaus zielt die Studie darauf ab, das Verständnis der immunologischen Funktion von Plasma-Osteopontin zu verbessern. Obwohl sechs Monate nach der Operation ein Rückgang der Osteopontin-Spiegel beobachtet wurde, war dieser Rückgang nicht statistisch signifikant. Um die Anwendbarkeit zukünftiger Forschungsergebnisse und die statistische Aussagekraft zu verbessern, empfehlen wir, die Stichprobengröße zu erweitern und die Zeitraum der postoperativen Verlaufsuntersuchungen zu verlängern.

2. Introduction

2.1 Main Introduction

One of the most common degenerative joint illnesses, osteoarthritis (OA) is defined by articular cartilage damage and gradual degeneration, along with corresponding anatomical and functional abnormalities in the afflicted joint.[1] Osteoarthritis of the hip (HOA) is the second most prevalent form of OA.[2] Similar to other types of OA, HOA is defined by reactive bone alterations and articular cartilage degeneration.[2] Clinical symptoms include groin discomfort, stiffness in the joints, and loss of function.[3] Reduced joint space, marginal osteophyte development, subchondral cysts, and subchondral sclerosis are radiographic indicators of HOA.[3,4]

Joint space width (JSW) and osteophytes may be measured without invasive procedures for the diagnosis of HOA using X-ray analysis.[4] Radiographic HOA may better minimize the subjectivity of HOA diagnosis and enhance sensitivity of detection compared to clinical categorization of HOA based on the presence of pain, either self-reported or upon physical examination of the joint.[4]

Physiological processes include tissue regeneration, angiogenesis, bone homeostasis, wound healing, cell adhesion, and immunological response all require the phosphoglycoprotein Osteopontin (OPN).[5,6] OPN was first discovered by Franzen and Heingard in the middle of the 1980s as a sialic acid-rich matricellular protein produced from the mineralized matrix of bovine bone.[7] OPN is a soluble protein found in human physiological tissues and is immobilized in the extracellular matrix of bone.[8]

OPN concentrations in the plasma and synovial fluid are greater in OA patients than in healthy people, according to certain studies.[9] OPN has been shown to enhance nuclear factor-kappa B (NF-kB) activity, which in turn raises the activity of inflammatory mediators such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a), and many others.[9] This upregulation of the inflammatory cascade is accomplished by the NF-kB and IL-1. Numerous studies indicate that a lack of OPN lowers chondrocyte apoptosis and angiogenesis in OA, preventing the degeneration of joint cartilage and joint swelling. OPN may be used as a biochemical marker to grade the severity and course of OA and may be helpful in predicting how the disease will develop.[10]

2.2. Study Objectives

This study measured plasma osteopontin levels in 30 patients with severe idiopathic hip joint arthritis, before and six months after they underwent total hip replacement surgery.

The results of this study aim to correlate between pre- and postoperative plasma osteopontin levels in order to demonstrate the response of the plasma level of osteopontin to the operation

and determine whether it is possible to predict the outcome and benefits of the total hip replacement surgery for individual patients based on these values. Furthermore, the study aims to enhance understanding of the immunological function of plasma osteopontin.

2.3. Osteoarthritis

2.3.1. Definition

Around 250 million individuals worldwide suffer from osteoarthritis (OA), one of the most prevalent painful and incapacitating illnesses.[11] It lowers patients' quality of life and burdens families and the community financially. OA presents a significant threat to social and public health, especially as the population ages and life expectancy rises.[12] All joint tissue types, including cartilage, synovial membrane, menisci, infrapatellar fat pads, and subchondral bone, are affected by OA, which is a whole-joint disease brought on by a combination of systemic vulnerability and local causes.[13] Numerous causes, including inflammation, mechanical, aging, and metabolic considerations all have a role in the etiology of OA, which eventually results in synovial joint function loss, articular structural degradation, and long-term chronic pain.[14-16]

In OA, the condition often worsens over time and usually develops gradually. The intensity and symptoms of this illness might subsequently deteriorate as a result of its stages or gradual progression over time.[17] Based on the identification of established causing factors, such as trauma, surgery on the joint structures, and deformed joints at birth, OA may be classified as primary (idiopathic) or secondary.[18]

2.3.2. Etiology

Causes of osteoarthritis (OA) are poorly understood. Instead of being brought on by a single illness state, OA is caused by a complex condition that is connected to a number of risk factors. The initiation and course of OA are significantly influenced by constitutional and biomechanical risk factors, despite the fact that the genes that cause it are well recognized.[19,20] To diagnose OA, a variety of diagnostic methods are performed, including a radiographic and clinical examination combination.[21]

2.3.3. Prevalence and Incidence

While the majority of research have focused on OA in certain regions, several others have provided data on OA prevalence and incidence more generally. 240 million individuals worldwide are estimated to be suffering with OA symptoms, with 10% of males and 18% of women in this age group (age 60 and older) affected.[22] 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, according to GBD estimations.[12] Compared to

1990, these numbers have grown by 9.3% and 8.2%, respectively. Several countries have done population-based OA prevalence and incidence investigations. Over half of English individuals over 50 reported OA in at least one joint, including the knee, hip, hand, and foot, in a large survey.[23] Based on screening questions that satisfied ACR clinical criteria, 29% of Spanish people over 20 had OA at one or more sites in a recent survey.[24] In Germany, 17.9% of persons over 18 report having osteoarthritis, with women experiencing a greater frequency (21.8%) than males (13.9%).[25]

Attention has also been drawn to multiple-joint OA (MJOA), which has been defined in at least 10 different ways.[26] Due to this variability, it has been difficult to reach consensus on the prevalence of MJOA. A comprehensive review revealed prevalence estimates that ranged from 5% to 25%. In general, MJOA has poorer OA-related outcomes compared to single joint involvement.[27]

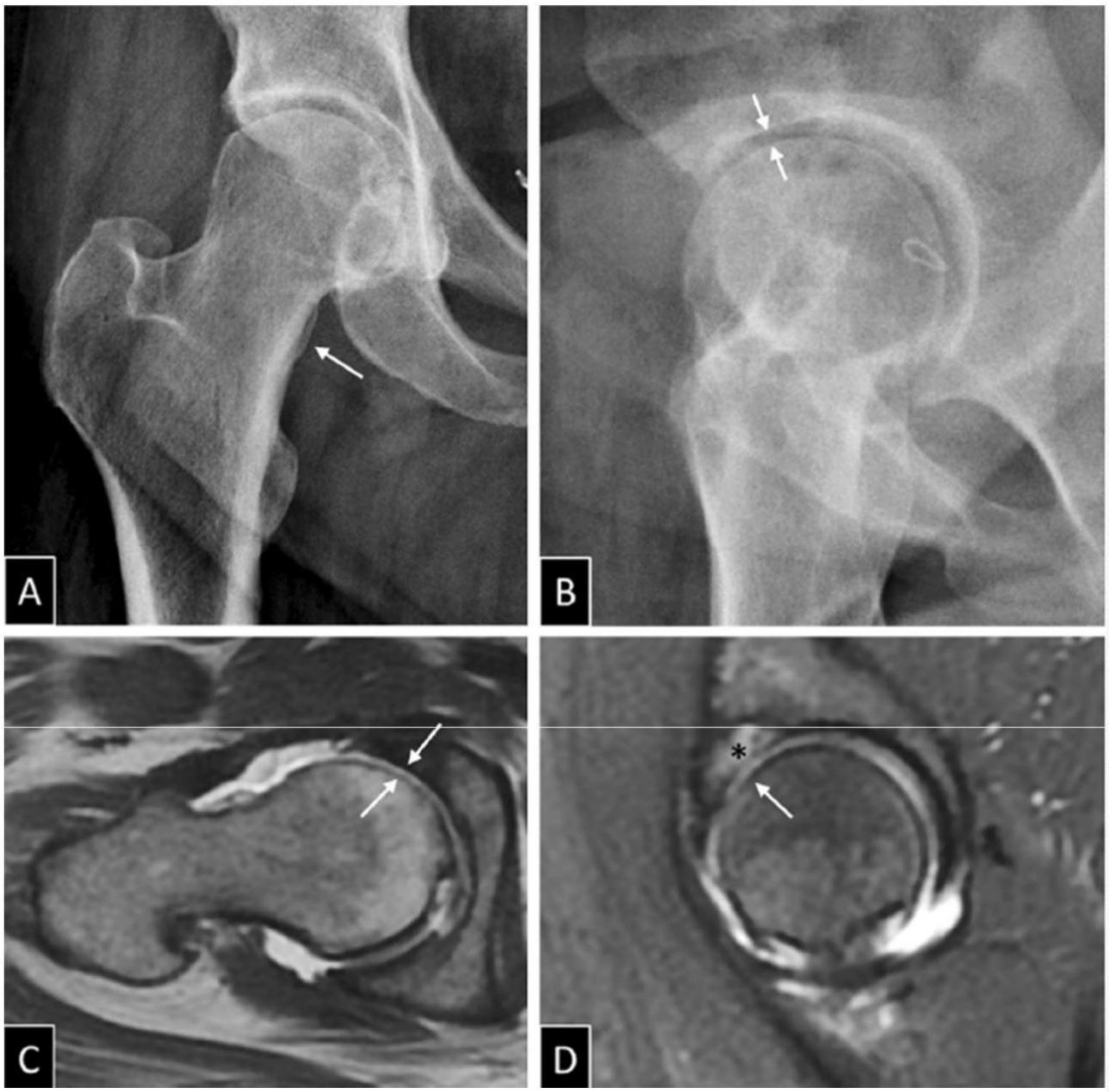


Figure 1: OA in right hip joint.[28]

2.3.4. Overview of Hip OA

After knee OA, hip OA (HOA) is the second most prevalent kind of OA. Similar to other types of OA, HOA is defined by reactive bone alterations and articular cartilage degeneration.[2] Clinical symptoms include groin discomfort, stiffness in the joints, and loss of function.[2] HOA radiographs show reduced joint space, marginal osteophyte growth, subchondral cysts, and sclerosis.[29,30] Joint space width (JSW) and osteophytes may be measured without invasive procedures for the diagnosis of HOA using X-ray analysis.[30] Compared to clinical categorization of HOA based on pain, either self-reported or on joint examination, radiographic HOA may reduce subjectivity of the diagnosis and increase the sensitivity. HOA tests have always had inconsistent requirements.[30-32]

In 2009, Dagenais and colleagues conducted a comprehensive analysis on radiographic HOA prevalence, which ranged from 0.9 to 27% globally. Risk factors did not affect prevalence.[33] Since then, a global estimate of HOA prevalence has not been consolidated, and subsequent studies have not offered a complete and rigorous examination of subgroup prevalence estimates by region, gender, and diagnostic approach.[31,33]

2.3.5. Risk Factors

Multifactorial risk factors, including systemic, socioeconomic, and biomechanical risk factors, can influence the development of osteoarthritis.[34] Compared to other multifactorial risk factors, some may be more controllable.[35]

Age-related alterations in the neurological response linked to proprioception[36], thinning of joint cartilage[37], diminished chondrocyte response in healing[38], and hereditary predisposition are all systemic risk factors for the development of OA[39]. High body mass index (BMI) and the hormonal variations linked with feminine gender are additional systemic risk factors.[35,40] Acetabular dysplasia causes biological changes that eventually lead to joint instability, and even after treatment, the disorder may still raise the possibility of developing hip OA.[41]

Physical workouts and activities including walking, long distance running, and weightlifting may all be biomechanical risk factors for the development of OA.[42] These tasks could put a repeated load on a joint with OA due to their physical demands.[43] Sports that require a lot of physical exertion might also raise your risk of injury or direct impact damage to your joints.[43] Injury-induced OA may result from trauma to the hip joint's supporting components, such as the acetabular labrum, which increases the strain on the opposing cartilage surfaces. When compared to other less physically demanding occupations, working in environments like farming, construction, and healthcare that require using heavy machinery and carrying heavier physical loads increases the risk of OA due to increased mechanical stress at specific joints like the hip.[44] As a result of the body's greater weight-induced stress on the hips, it has also been

hypothesized that a higher BMI increases the risk of hip OA.[45] Obesity is thought to be one of the most important risk factors in the onset and progression of OA for weight-bearing joints due to abnormal mechanical demands on the joint, chronic inflammation, and cartilage degeneration as a result of increased body mass.[46] This risk factor is potentially modifiable. People with OA often exhibit low levels of physical activity, which is a controllable biomechanical risk factor.[47] The lower stimulation of cartilage degradation and bone remodeling may be related to this. Exercise and free-living physical activity have been demonstrated in the past to enhance BMI, body composition, and bone integrity.[48]

. Age: The most significant risk factor for OA is age. At all joint locations, radiographic OA prevalence increases with advancing age.[49] Radiographic evidence of severe OA in the hands or feet was found in 10% to 20% of Dutch women between the ages of 40 and 50, and in around 75% of those over the age of 70. Numerous reasons might be used to explain this.[50] Articular cartilage is made up of a single cell type called chondrocytes, which stop producing extracellular matrix components including aggrecan and collagen type II as they age and instead express more matrix metalloproteinase. In addition, a buildup of reactive oxygen species (ROS) causes mitochondrial malfunction and chondrocyte death.[51]

. Gender: The frequency and incidence of hip osteoarthritis (OA) varies significantly between men and women, making gender an important risk factor. According to studies, women are more prone than males to develop hip OA. For example, the lifetime risk for symptomatic hip OA is 18.5% for males and 28.6% for females, according to the Centers for Disease Control and Prevention.[52]

Furthermore, studies show that hip OA is more common in women than in males as people age, particularly beyond the age of 55. According to a study, women between the ages of 70 and 75 were 37% more likely than males in the same age range to develop hip OA.[53]

These results emphasize how crucial it is to take gender variations into account when diagnosing and treating hip osteoarthritis.

. Obesity and Metabolic Factors: Obesity is a known risk factor for osteoarthritis, including hip osteoarthritis, that can be changed. Weight gain causes weight-bearing joints to experience higher mechanical stress, which speeds up cartilage deterioration. According to a research by Coggon et al., those who have a body mass index (BMI) of more than 30 kg/m² are much more likely to develop knee OA, and similar correlations have been shown for hip OA.[54] Obesity often co-occurs with metabolic syndrome (MetS), which is defined by disorders such as insulin resistance, dyslipidemia, and hypertension. MetS and obesity together have been shown to

increase the risk of hip OA. According to a research by Cheng et al., obesity, which has been linked to a higher risk of lower limb OA, commonly co-occurs with metabolic dysregulation.[55]

. Physical Activity: High-impact sports, as well as the subject's joint health, have been linked to an increased risk of osteoarthritis (OA), whereas low-impact sports, as well as those performed by persons with normal joint structure and neuromuscular function, have been linked to a reduced risk of OA.[56]

Running is not associated with OA in young, low-BMI runners.[57] While engaging in any form of physical activity that involves torsion and impact loading, prior joint injury or surgery, people with abnormal joint anatomy or alignment, disturbances of joint or muscle innervations, articular surface incongruity or dysplasia, joint instability, or insufficient muscle strength are more likely to develop OA. On the contrary, weight lifters and soccer players have shown a higher incidence of OA, probably as a result of the weight lifters' typical high BMI and the soccer players' history of knee injuries.[57]

. Joint Injury: Hip osteoarthritis (OA) is significantly increased by joint trauma. This relationship has been the subject of several studies. In a case-control study, the odds ratio for hip OA was 4.3, indicating that prior hip injury increased the risk of hip OA.[58] This implies that the risk of developing hip OA is more than four times higher for those who have had hip injuries in the past than for those who have not. According to another research, joint damage significantly raised the chance of developing osteoarthritis later on at the location of the injury, with a hip relative risk of 3.50.[59] Clinicians are advised by clinical guidelines to take prior hip joint injuries into account as a risk factor for hip osteoarthritis.[60]

2.3.6. Symptoms

Clinical symptoms and structural findings of OA often conflict. For example, a person with large osteophytes and little joint space left on X-rays but with only relatively minor symptoms.[61] Conversely, a person with minimal or no structural abnormalities on an X-ray may yet suffer significant symptoms. However, there is often a correlation between discomfort and radiographic disease severity.[62]

In the afflicted joint or joints, patients with OA often complain of pain and stiffness. After a lengthy period of sitting, stiffness is worse in the morning or when you first get up. It becomes better after 30 minutes. Early in the course, pain is use-related, but it might eventually become less predictable. Despite the common perception that OA is a progressive illness, natural history studies demonstrate that most patients report no change in symptoms after 6 years of monitoring.[63]

2.3.7. Diagnosis

In-depth information on the effectiveness of physical examination techniques in the diagnosis of hip OA, as well as a video presentation of the hip examination, were recently reviewed.[64] Both restricted hip adduction and hip internal rotation of less than 15° are fairly sensitive (66%) and specific (72%).[64,65] Hip internal rotation pain has a higher sensitivity (82%) but a lower specificity (39%).[65]

Radiographic osteophytes are sensitive (89%), specific (90%). Hip pain and an osteophyte are also sensitive (89%) and specific (90%).[65] These data suggest that medical history and physical examination may establish a preliminary hip or knee OA diagnosis.

Radiographs reveal structural deterioration caused by osteophytes or joint space constriction. Radiographs may indicate osteophytes before OA symptoms.[29] Thus, conventional radiography does not exclude OA. If clinical presentation strongly supports OA, physicians should start treatment despite normal radiographs.[29]

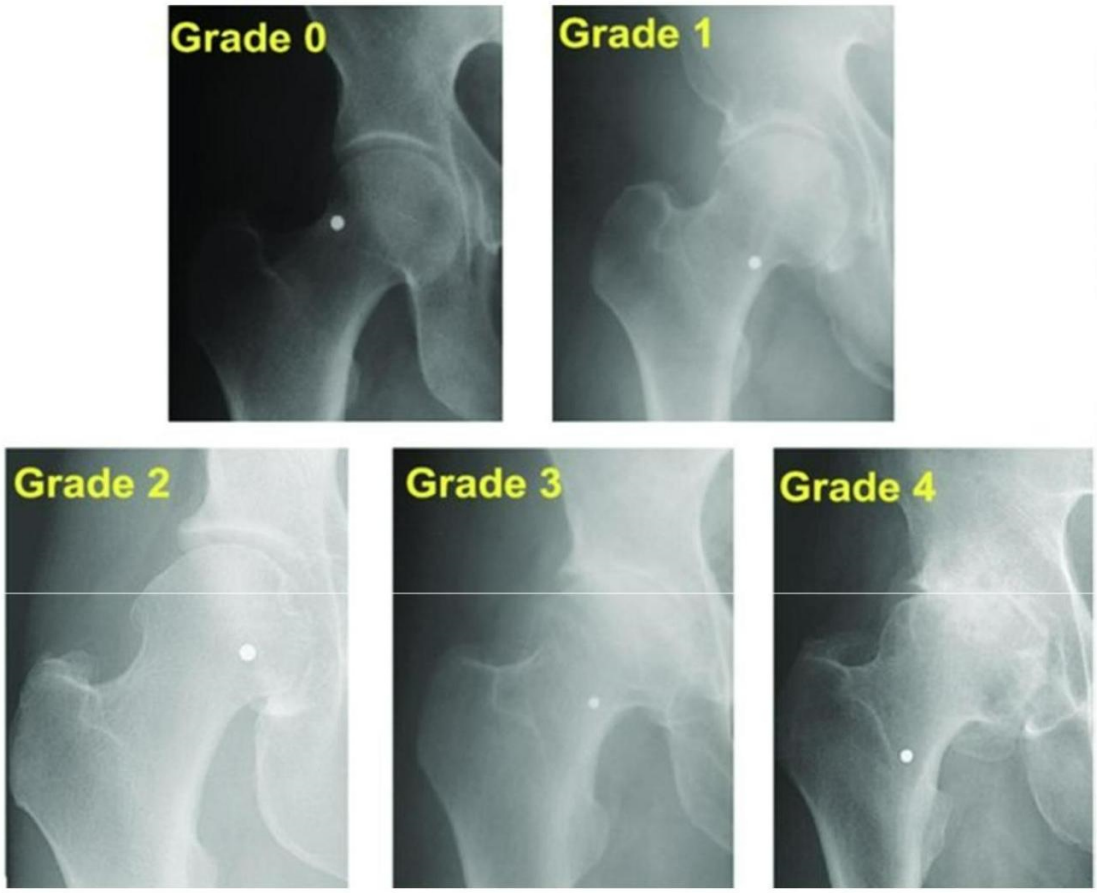


Figure 2: Example plain radiographs showing the Kellgren and Lawrence radiographic hip osteoarthritis severity grading.[66]

A lateral image and an anteroposterior view are often included in hip radiographs. It is not required to carry any weight. Hip radiographs have strong inter- and intra-observer reliability for spotting joint space narrowing. Compared to radiographs of the chest or knee, hip radiographs expose the patient to more ionizing radiation.[67]

Magnetic resonance imaging is rarely necessary for diagnosing or treating knee or hip OA. A more complete view of pathological involvement is provided by magnetic resonance imaging, which recognizes abnormalities in cartilage, meniscus (knee), labrum (hip), bone, and synovium.[68] MRI is helpful for research investigations to detect early OA and track structural changes over time because of its great sensitivity. If there is a suspicion of a disease that would need different and more immediate treatment than OA, such as a subchondral insufficiency fracture, tumor, or infection, an MRI might be helpful in clinical management.[68]

Osteophytes, joint effusion, and other characteristics may all be seen with ultrasound.[69] In comparison to MRI, ultrasonography offers osteophyte detection sensitivity and specificity over 85%. When measuring joint space narrowing, ultrasound is not as precise as MRI. In Europe and an increasing number of US hospitals, ultrasonography is used regularly to diagnose OA and monitor its development since it is less costly and more portable than MRI.[70]

Even while laboratory test results are often normal in OA patients, they may still be useful in narrowing the list of alternative diagnoses in cases when the diagnosis is uncertain. Testing for autoimmune disorders and systemic inflammatory diseases may be done using C-reactive protein levels and erythrocyte sedimentation rate. Gout might be diagnosed using the amount of uric acid. Clinical guidelines from the American College of Rheumatology caution against frequently administering arthritis panels to anyone with joint problems.[71]

2.3.8. Treatment

(1) Pharmacotherapy: The medications most often suggested in the recommendations are NSAIDs and paracetamol.[72] A 2017 meta-analysis indicated that paracetamol, the first-line pain medication for osteoarthritis, was ineffective as a single agent owing to its tiny effect sizes compared to placebo and safety concerns.[73] Topical NSAIDs outperformed placebo for osteoarthritis pain in a 2018 meta-analysis.[74] There haven't been any significant gastrointestinal or renal side effects associated with topical NSAIDs so far in clinical studies or in the general population.[74]

Oral NSAIDs have shown clinically significant pain and function improvements in published studies.[72] However, safety is a crucial factor to take into account when choosing the formulation and dosage for certain individuals, and oral NSAID usage is ideally limited to short-term use at the lowest dose.[73]

Injections of intra-articular corticosteroid are often used to treat hip osteoarthritis (OA) pain.

According to research, these injections may increase function and provide temporary pain relief. Intra-articular corticosteroid injections may be useful in the short term for lowering hip OA pain, according to a systematic review.[75] However, the quality of the evidence was not very high, and more thorough studies are required to confirm the benefits and ascertain how long they will last. Although these injections may provide pain relief and functional improvement, another study pointed out that the benefits are often transient, and that further research is needed to determine the best dose and frequency.[76] Concerns have also been raised about possible side effects from intra-articular corticosteroid injections, such as faster OA development and joint destruction. Before giving these injections, a study from an expert group highlighted the need of carefully choosing patients and weighing risks and benefits.[77]

In conclusion, hip OA patients may have short-term pain relief with intra-articular corticosteroid injections, but it is yet unknown whether these treatments will be safe and effective in the long run. When proposing this medication, clinicians should take the patient's unique circumstances into account and balance the possible advantages against the hazards.

Duloxetine, a serotonin and norepinephrine reuptake inhibitor, is used to treat refractory pain.[78,79] A meta-analysis of three trials found that duloxetine had controllable side effects and a clinically meaningful reduction in symptoms after three months of treatment for knee osteoarthritis.[79] Duloxetine's ability to lessen discomfort and enhance function has been supported by two sizable studies that were conducted in China[80] and Japan[81] in 2017. Further research is necessary to determine if this kind of intervention is particularly useful in people with neuropathic or central pain involvement.

In individuals with osteoarthritis, tramadol or tramadol + paracetamol reduces symptoms and improves function, although these advantages are modest, according to a meta-analysis.[82] A 2014 meta-analysis of non-tramadol opiates found that their little average benefit is accompanied by considerable increases in the risk of adverse events, and the reported advantages for pain outcome were of uncertain therapeutic significance.[83] Direct comparisons of opiates and non-opiates for osteoarthritis or lower back pain showed that non-opiates were more effective and opiates were more harmful.[84] Up until 2014, most recommendations were unclear on the use of opiates; however, more recently, the marginal benefit weighed against the adverse effects, addiction danger, and overdosage risk has resulted in a general deterrence of prescribing these drugs to osteoarthritis patients.[72,78,85,86]

(2) Lifestyle and Behavioral Interventions: Self-management training, exercise, weight loss if overweight, and walking are the guidelines' first-line treatments.[72,78]

On a variety of issues crucial to patient education, including information on the various treatment options, information on the condition, information on the pathophysiology, and information on diagnostic imaging, experts and patients have come to agreement.[87]

In the last ten years, high-quality data has been available showing the benefits of exercise treatment in reducing pain and increasing joint mobility, with estimated effect sizes of 0.4 – 0.5 for hip osteoarthritis.[88,89] The problem is to have this treatment broadly adopted and to improve long-term adherence, although exercise therapy is increasingly recognized as one of the main components of managing osteoarthritis. Modifiable obstacles and facilitators to deliberate exercise include a person's location or environment that encourages or discourages exercise skills and abilities, independence, social competence, and adaptable behavior.[90] Discrimination regarding exercising are another obstacle.

Weight reduction interventions for overweight or obese people with knee osteoarthritis had an effect size of 0.37.[91] There is unmistakably a dosage response relationship between the amount of weight loss and the impact on pain and function, according to many investigations.[92,93] Studies comparing the benefits of nutrition and exercise on pain and function in people with arthritis found that the combination of the two was superior than either treatment alone.[92,93] The long-term maintenance of weight reduction is the issue for this technique.

(3) Surgical Intervention: Candidates for total hip replacement (THRs) have advanced radiographic abnormalities, chronic discomfort, functional loss, and/or both.[29] Each year, the US performs more than 700000 primary TKRs and 330000 primary THRs, more than 90% of which are done for OA.[94] Less than 5% of people have significant difficulties at 90 days, and 90-day mortality is less than 1%.[95-97] Following recovery from these surgeries, around 90% of THR and 80% of TKR patients report having little to no post-procedure discomfort.[98]

According to randomized clinical research comparing TKR with a demanding physical therapy regimen, individuals who had TKR saw improvements of 35 points on a scale from 0 to 100 on the Knee Injury and Osteoarthritis Outcome Score as opposed to 17 points in those who received physical therapy.[99] Over a 20-year period, less than 10% of TKRs and around 20% of THRs need revision.[100,101]

Younger and more active patients, those with comorbid conditions, those treated in low-volume hospitals, and those operated on by low-volume doctors all had greater failure rates.[102,103] People who have THR beyond the age of 70 are significantly more likely to pass away with their original implants in situ than they are to need revision because of the typically low revision rates.[104] In individuals with OA with a symptomatic meniscal tear for whom nonoperative treatment was unsuccessful, arthroscopic partial meniscectomy has a restricted use. Arthroscopic debridement is not suitable for treating OA.[105-107]

2.4. Osteopontin

Physiological processes include wound healing, angiogenesis, cell adhesion, tissue regeneration, bone homeostasis, and immunological response all require the phosphoglycoprotein osteopontin (OPN).[108,109] OPN was first discovered by Franzen and Heingard in the middle of the 1980s as a sialic acid-rich matricellular protein produced from the mineralized matrix of bovine bone.[110] Oldberg and colleagues named this sialoprotein "osteopontin" from the Greek words "osteon" meaning bone, and "pons" meaning "bridge". The authors claim that this name more accurately captures the potential function of OPN, which is a byproduct of cells in the osteoid matrix.[109,111,112] OPN is confined in bone matrix as an extracellular matrix (ECM) protein and soluble protein in human physiological tissues.[113-116]

Human OPN is encoded by SPP1, a member of the SIBLING (Small Integrin Binding Ligand N-linked Glycoprotein) family, which also contains dentin sialophosphoprotein, bone sialoprotein, dentin matrix protein 1, and matrix extracellular phosphoglycoprotein.[109,117,118] All SIBLING proteins on human chromosome 4q21 have exon structures with an Arg-Gly-Asp (RGD) sequence.[118] SPP1 on 4q21-q25 has an open reading frame of 942 nucleotides and three mRNA variants, OPN-a, OPN-b, and OPN-c. OPN-a has all exon coding information, OPN-b lacks exon 5, and OPN-c deletes exon 4.[119-121] However, alternative splicing produces two forms of the OPN transcript: OPN-4, which lacks exons 4 and 5, and OPN-5, which has an exon 3-derived portion.[122]

The pathogenic process and therapeutic response in disorders with a genetic component are influenced by the mRNA alternative splicing of certain proteins.[123] OPN splicing variations have been discovered to have a part in the immunopathogenesis of various different illnesses, including cancer, in humans. OPN isoforms have been shown to be tissue-specific in illness and to affect signaling pathways based on the availability of ligands supplied by the microenvironment.[123]

OPN is an essential intrinsic regulator that plays a key role in the onset and progression of OA. OPN levels are higher in the synovial fluid and plasma of OA patients compared to healthy individuals, which may suggest a link between OPN and the severity of the disease's joint lesions.[124] The concentration of OPN in the OA group was significantly greater than in the control group, and there was also a gender difference between the two groups, according to Min et al.'s analysis of the serum of 249 people.[125] OPN gene polymorphism may reduce OA risk.[126] They found a strong link between higher OPN mRNA and protein expression in OA patients' synovial fluid and disease progression.[127] Recent investigations have indicated that OA patients' superficial and deep articular cartilage have significantly elevated OPN expression.[128,129] In animal studies, elevated OPN expression enhances subchondral bone blood ves-

sel formation, facilitates articular cartilage degeneration induced by metabolism, and accelerates OA progression.[130] It accelerates OA subchondral bone remodeling and turnover. Contradictory evidence suggests that OPN may treat OA. The OPN/CD44/PI3K signaling pathway may also inhibit chondrocyte degeneration and cartilage matrix component loss through binding to CD44 and integrin.[131] OA chondrocytes express more OPN, CD44, and mRNA. Hyaluronan (HA) and OPN are CD44's primary ligands, which interact with various ECM components.[132] CD44 variants with exons v6 and v7 bind to the N- and C-terminal regions of OPN to control bone metabolism independently of arginine-glycine-aspartic.[133] The elevated expression of OPN mRNA in OA may be brought on by an increase in HA levels in the synovitis, which would eventually lessen the severity and improve the symptoms of OA, according to Zhang et al.[134] OPN deficiency may speed up the development of chondrocytes and increase the severity of OA. It may also increase the production of pro-inflammatory chemicals and decrease the expression of COL2A1.[135]

2.5. Role of Osteopontin in Osteoarthritis

2.5.1. Role of Osteopontin in the Immunopathology of OA

Macrophages, dendritic cells (DC), T cells, and NK cells release OPN, a T cell helper 1 (TH1) cytokine involved in immunological responses. It also acts as a pro- and anti-inflammatory molecule, causing DCs and macrophages to migrate to the site of inflammation and suppressing iNOS and NO production.[136] OPN was originally called Eta-1 (early T lymphocyte activation gene 1) because it is expressed in activated T cells and regulates T cells to generate immunological responses.[137] Inactivated T cells produce SPP1 through T-bet (T-box transcription factor necessary for CD4+ T helper cell lineage control), which is essential for TH1 skewing.[137,138] In macrophages, pro-inflammatory cytokines including IL-1, IL-6, tumor necrosis factor-alpha, and interferon-gamma, as well as biomolecules like angiotensin-II, oxidized LDL, and phorbol-ester, produce OPN.[138,139]

OPN regulates macrophage accumulation and retention at injury sites and promotes phagocytosis, both of which are essential for macrophage function. Additionally, OPN functions as a strong chemoattractant, encouraging macrophage migration and increasing the production of IL-12, while inhibiting apoptosis and the production of IL-10 via interactions with CD44, integrins 4 and 9, and other molecules.[120,138,140,141] The SPP1 promotor may increase OPN expression in macrophages that have been activated by lipopolysaccharide (LPS).[142] OPN prevents macrophages from presenting a widespread distribution of CD44, which inhibits the synthesis and movement of cytokines.[141] OPN improves DC maturation and motility through CD44 and v integrin binding, whereas inhibiting it increases apoptosis and lowers MHC class II expression. OPN increases CD80/86, MHC class II, and ICAM-1, which helps DCs polarize TH1.[120,141]

OPN is regarded as a multifunctional protein that contributes to the emergence of inflammatory disorders because it exerts a TH1 cytokine action.[141]

Collectively, these investigations into OPN's function and regulatory influence on inflammatory activity in OA have led researchers to conclude that changes in OPN expression or levels in chondrocytes and synoviocytes may cause metabolic disturbance in bone disorders.

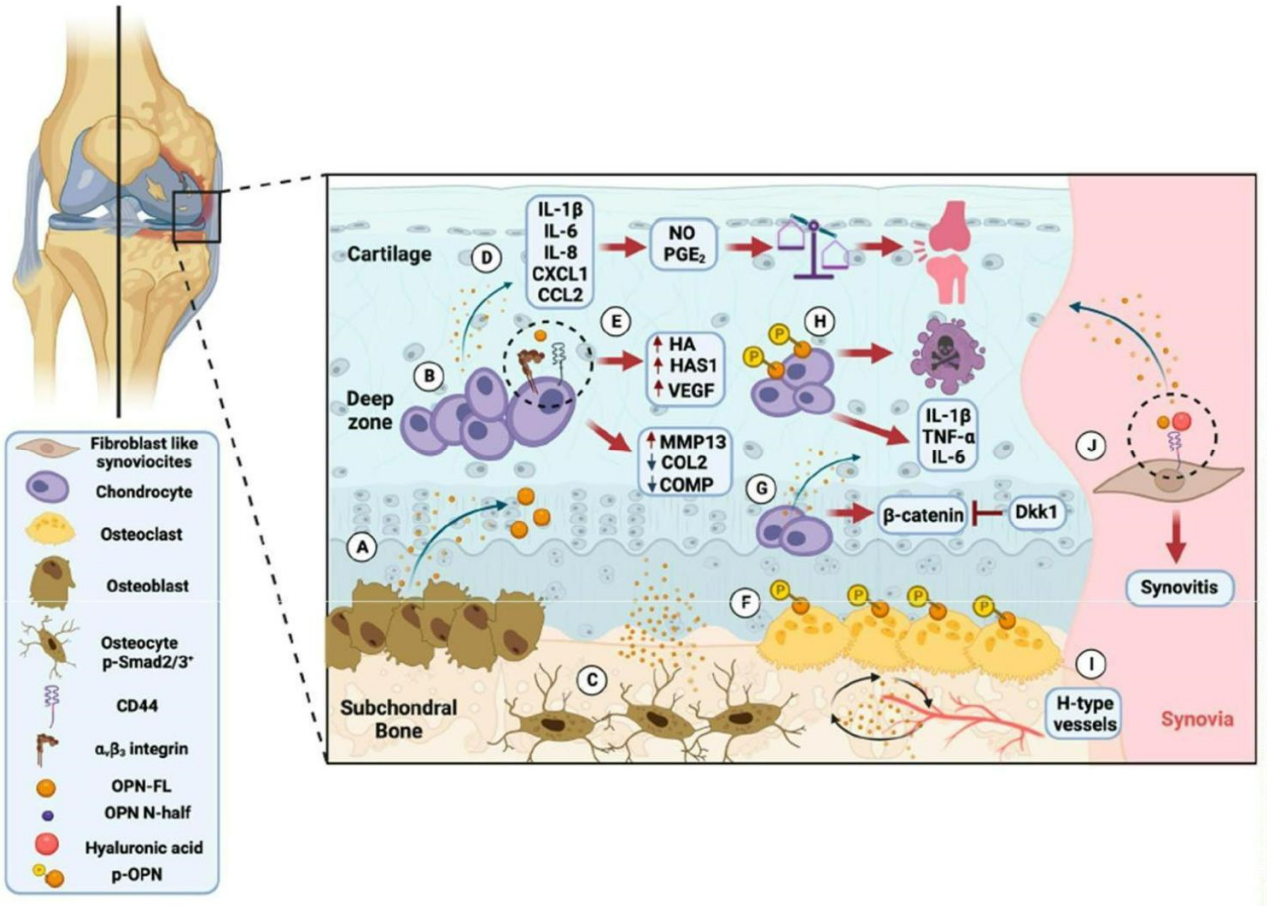


Figure 3: Role of osteopontin in the immunopathology of osteoarthritis.[143]

2.5.2. Role of Osteopontin in Metabolic Processes in OA

OPN is released by a variety of cells, including synovial cells, chondrocytes, lymphocytes, vascular smooth muscle cells, epithelial cells, and macrophages, which are all present in various tissues and cells.[144-146] It is widely documented that abnormal OPN expression, either at the mRNA or protein level, is linked to the onset of OA. OA is exacerbated by phosphorylated OPN in chondrocytes and synovial fluid, as well as by elevated OPN.[144,147,148] Recent studies suggest that OPN overexpression may slow the degenerative development of OA by increasing chondrocyte proliferation and decreasing their death through the NF-kB signaling pathway.[146] In CIA mice, increasing blood OPN levels correlate with increased numbers of tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts and bone degradation, whereas silencing OPN using lentiviral-OPN short hairpin RNA had the reverse effect.[149] S-allylcysteine,

which reported by Elmazoglu et al., reduces IL-1b and IL-6 in chondrocytes, as well as the inflammatory response, which in turn reduces the severity of OA.[150] Cartilage disintegration and subchondral bone remodeling are both mediated by OPN in OA.[151] In anterior cruciate ligament transection and medial meniscus OA model, increased OPN secreted by pre-osteoblasts and osteoblasts in subchondral bone may promote osteoclastogenesis and blood vessel formation, accelerate bone turnover and remodeling, and mediate articular cartilage degeneration caused by bone metabolism.[151] Together with the abnormal expression of Sox9, Runx2, and OCN, OPN plays a role in the development of osteogenic and chondrogenic differentiation and may contribute to metabolic disruption and cartilage deterioration in OA.[152,153]

Due to its important role in regulating the metabolism of chondrocytes, synovial cells, and subchondral bone, OPN should be carefully managed at the optimum level to prevent the development and progression of OA.

2.5.3. Pharmacological Considerations of Osteopontin in OA

OPN has a complex influence, making it challenging to manage its expression. Recent research has examined how OPN impacts OA in relation to both new and old drugs. Pharmacological OA treatments have focused on OPN levels in chondrocytes, synovial tissue, and synoviocytes.[154] S-allylcysteine suppresses chondrocyte IL-1b, IL-6, and OPN through lowering p-JNK/pan-JNK signaling, according to Elmazoglu et al.[150] OPN and these cytokines reduced OA progression by upregulating type-II collagen and peroxidase. In OA, Li et al. examined chitosan oligosaccharides in extracellular vesicles.[152] They observed that chitosan oligosaccharides inhibited viability and migration while reversed IL-1b-induced chondrocyte death.[155] Additionally, they discovered that chitosan oligosaccharides reduced cartilage injury by upregulating OCN, Col2a1, and Runx2 through the PI3K-Akt pathway and downregulating OPN, p53, and IL-1b. By regulating the level of OPN in rats, isorhamnetin also greatly reduced the damage to the articular cartilage and, therefore, MIA-induced knee edema.[155]

Isorhamnetin suppressed OPN, iNOS, NO, COX-2, and PGE2 to arrest OA development. Slovacek et al. found higher OPN and MMP-9 in OA.[156] IL-1, IL-6, and CRP enhance OPN and MMP-9. Adiponectin stimulates the synthesis of OPN in synovial tissue, which, according to prior study, accelerates bone degradation. CIA mice with lentiviral-OPN short hairpin RNA silencing may have fewer TRAP-positive osteoclasts and less bone degradation. The microRNA (miR) may also have an impact on how OPN is expressed in OA. MiR-181c may dramatically lessen the effect of OPN on increasing MMP-13, IL-8, and IL-6 production and inhibit synoviocyte proliferation as a therapy for OA. At the end, this would lessen joint cartilage degeneration and local inflammation.[156]

Early OA diagnosis has received more attention recently, and conventional therapy has improved the prognosis, although OA treatment is still insufficient. A greater understanding of the

pathogenic process of OA is required to develop cutting-edge therapeutic strategies. To successfully prevent and cure OA, the right mediators of joint deterioration must be found.[157] OPN has been often found in high concentrations in the plasma and synovial fluid of OA patients, suggesting that it may be a possible biochemical diagnostic for the diagnosis of OA.[144,158,159] In a recent study, Abdelnaby et al. suggested using OPN as a diagnostic and predictive technique to evaluate the severity of OA symptoms.[160] The use of biochemical markers has been suggested as a way to identify the illness early, evaluate its severity, and provide safe and effective disease-modifying medications to OA patients. Therefore, OPN could be a useful diagnostic biomarker for the identification and treatment of OA.

3. Materials and Methods

3.1. Study Design

This was a prospective observational study. The study involved determination of plasma level of osteopontin pre- and postoperative for 30 patients with severe idiopathic hip joint arthritis who were planned for total hip replacement surgery. The osteopontin level was measured in patients before the operation and six months postoperatively. The results of this study aim to correlate between pre- and postoperative plasma osteopontin levels in order to demonstrate the influence of operation on the plasma osteopontin level and determine whether it is possible to predict the outcome and benefits of the total hip replacement surgery for individual patients based on these values. Furthermore, the study aims to enhance understanding of the immunological function of plasma osteopontin.

3.2. Patient Selection

The patients were recruited from the orthopedic outpatient clinic in Mühlenkreiskliniken Lübbecke. All patients were detailed informed about the procedure prior to surgery. The participants signed a consent form, agreeing to participate in the study. Detailed informed consent forms and discussions were ensured comprehensive information for study participants.

3.2.1. Inclusion Criteria: Eligible patients of both genders aged over 50 years with severe idiopathic osteoarthritis of the hip joint according to the American College of Rheumatology (ACR) criteria; (grade III and IV according to the Kellgren-Lawrence score), who were candidates for total hip replacement surgery. A uniform distribution of demographic data of the patients was preferred.

3.2.2. Exclusion Criteria: Patients with:

A. Osteoporosis
B. Non-degenerative arthritis, such as rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, gout, infectious arthritis
C. History of trauma or surgery on the affected hip joint
D. Autoimmune diseases
E. Malignant disease
F. Osteoarthritis in another joint or in the other hip side

3.3. Data Collection Methods

All Patients underwent the following Procedures

- Complete medical history: Gender, age, occupation, comorbidities, main complaint of hip pain, joint swelling, other joint stiffness, joint diseases, autoimmune diseases, malignant diseases, and history of trauma.

- Detailed clinical examination: Assessment of weight and height (with calculation of BMI). Examination of hip joint for tenderness, warmness, swelling, deformities, range of motion and muscle atrophy. Examination of small joints of hands and feet, shoulder-, knee- and ankle joints.

- Laboratory investigations: Measurement of osteopontin levels in plasma using an enzyme-linked immunosorbent assay (ELISA). Correlation preoperatively and six months postoperatively after total hip replacement surgery. Blood samples were taken from all patients, centrifuged, and stored at ≤ -20 °C until analysis.
  All laboratory examinations are conducted at Laborkrone in Bad Salzuflen.

- CRP (C-reactive protein) levels before and after surgery.

- Routine preoperative laboratory tests: CBC (complete blood count), electrolytes, liver- and kidney function tests.

- Radiological examinations: X-ray of the affected hip joints in two planes (anteroposterior and lateral) to determine the severity of the osteoarthritis were performed. The severity were determined according to the Kellgren-Lawrence score. 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, definite 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 (Kellgren and Lawrence, 1957).

3.4. Statistical Analysis

All analyses were performed with IBM SPSS version 25 software. Descriptive statistics were performed for sociodemographic characteristics. Normality test was conducted. Paired sample t-test was used to compare OPN level between pre and post operative. A P value .05 was considered to indicate statistical significance.

The statistical analysis for the study was performed by Dr. Ramy Abdelnaby from the department of neurology at Aachen University.

3.5. Ethical Considerations

. Approval

The study has received ethical approval from the Research Ethics Committee in Cologne University. All recommendations which ensuring that the study adheres to the highest ethical standards and protects the rights, safety, and wellbeing of the participants, werer followed.

. Data and Privacy Protection

To protect the privacy of study participants, the data were anonymized. All patients provided a general consent for the use of medical data upon admission. The participant's data were then deleted. The physicians and technical assistants involved in the study are bounded by confidentiality obligations.

. Documentation

Standardized documentation forms were used for secure data collection. Digital data were stored on a secure device and were accessible exclusively with a password. Data storage, processing, and analysis were conducted only in anonymous form. Re-identification of anonymised data is not possible.

4. Results

4.1. Analysis of Sociodemographic Data

A total of 30 patients were enrolled in our study, 16 of them are male, mean age of the patients is 74.3 years with BMI of 27.6 as shown in Table 1.

Table 1: Sociodemographic data of the patients:

Variable	N (%)
Gender **Male** **Female**	 16 (53.3) 14 (46.7)
Age (Y)	74.3(8.5) *
BMI (Kg/m^2)	27.6 (5.3) *
ASA **2** **3** **4**	 18(60) 10(33.3) 2(6.7)

*Mean (SD)

4.2. Comorbidities and Risk Factors

Concerning comorbidities and risk factors of the patients; 22 of them are hypertensive, 10 have coronary heart disease and 7 have hypothyroidism. Other comorbidities are shown in Table 2.

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

Comorbidities	N (%)
DM	3(10)
Hypertension	22(73.3)
Smoking	4(13.3)
Renal Failure	1(3.3)
Arrhythmeia	2(6.7)
Coronary heart disease	10(33.3)
Apoplex	0
Thrombose	1(3.3)
Pulmonary embolism	0
Hypothyroidism	7(23.3)
COPD	3(10)
Depression/psychosis	2(6.7)
Blood transfusion	0

4.3. Pre and Post Operative OPN and CRP

. Pre-Operative evaluation of plasma OPN level among hip surgery patients ranged from 12 ng/ml to 167.2 ng/ml with a mean level of 87.4 ng/ml. Meanwhile, the 6 months post operative mean level reduced to 78.5 ng/ml as shown in Table 3.

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

	Preoperative		6 months post operative	
Labs	Mean (SD)	Range	Mean (SD)	Range
Plasma OPN (ng/ml)	87.4(37.4)	(12-167.2)	78.5(37.3)	(10.9-165.4)

OPN: Osteopontin, SD: standard deviation

. A comparison between levels of OPN in hip surgery patients (pre-operatively) and normal values revealed a non-statistically significant difference P value 0.37 Table 4.

Table 4: Comparison between levels of OPN (pre-operatively) and normal values:

Variable	Preoperative Mean (SD)	Normal reference Mean (SD)	P value
Plasma OPN (ng/ml)	87.4(37.4)	94.8(24.9)	0.37

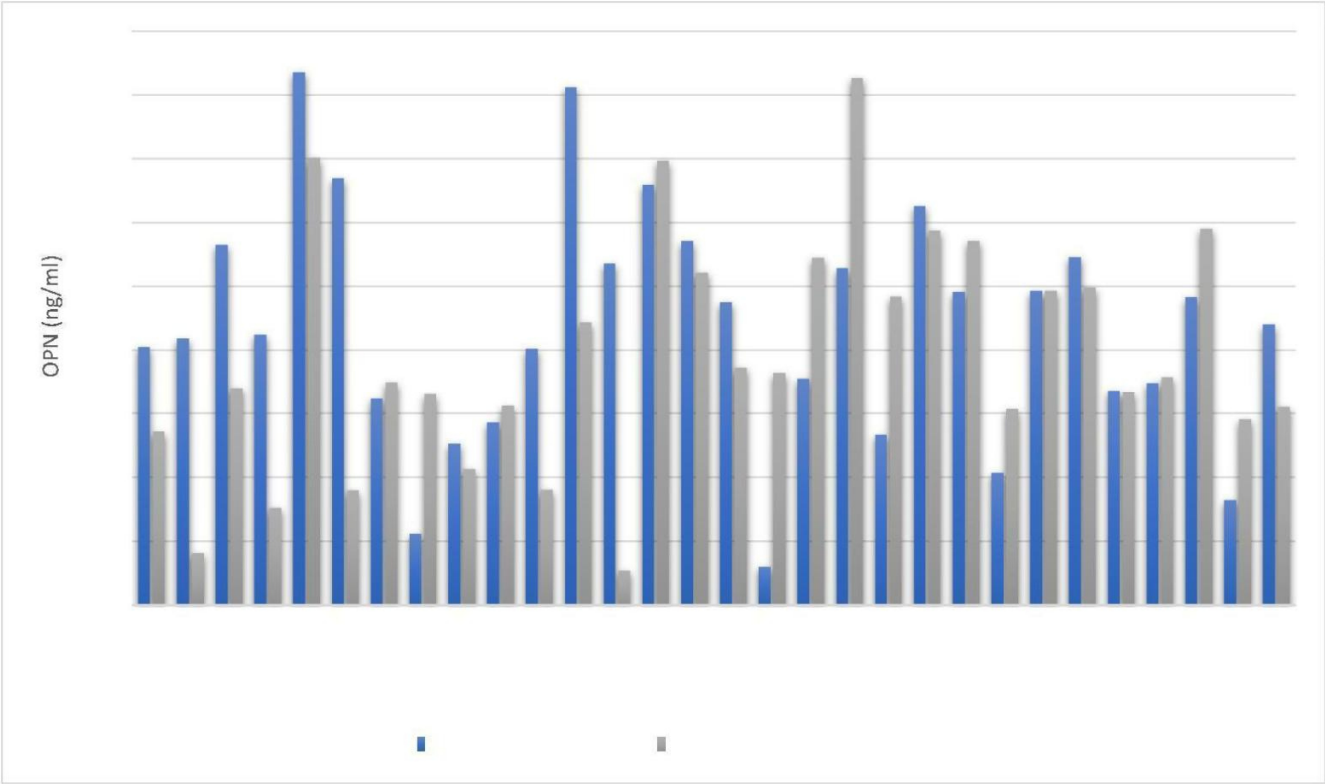
. Pre and post operative evaluation of CRP is done to exclude post operative infection to match our criteria. Preoperative CRP ranged from 0.6 (µg/ml) to 15 (µg/ml) with a mean level of 3.4 (µg/ml) whereas postoperative mean was 45.4 (µg/ml) as shown in Table 5.

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

	Preoperative		Post operative	
Labs	Mean (SD)	Range	Mean (SD)	Range
CRP (µg/ml)	3.4(3.3)	(0.6-15)	45.4(29.4)	(11.9-117.4)

CRP: C reactive protein, SD: standard deviation

Figure 4: Pre and post operative OPN value:



4.4. Paired Sample t Test

We conducted paired sample t test to study difference in OPN between pre and post operative, results showed that there is not a statistically significant difference in OPN between pre and post operative Table 6.

Table 6: Paired sample t test to identify the difference in OPN between pre and post operative in hip surgery:

Variable	T test	P value
Plasma OPN	-1.2	0.254

5. Discussion

5.1. Main Discussion

O-glycosylated phosphoprotein osteopontin (OPN) is produced in a variety of cells and tissues before being released into physiological fluids. OPN is a topic of interest in biomedical research because of its variety of roles, particularly when viewed in relation to immune responses and tissue healing processes. Particularly, its ability to interact with widely distributed multiple receptors emphasizes its significance as an active participant in a variety of physiological and pathological processes, including tumorigenesis, bone turnover, wound healing, inflammatory processes, ischemia, and immune responses.[161] A vital aspect of OPN's role is its ability to modulate immune responses at several levels. As an example, it exhibits chemotactic characteristics that enhance the migration of cells to areas of inflammation. Moreover, aside from its chemotactic properties, it serves as an adhesion protein that aids in cell adhesion and the progression of wound healing. Lastly, OPN mediates the activation of cytokine production through interaction with cellular signaling pathways. Therefore, an increase in OPN expression can result in the stimulation of pro-inflammatory cytokine synthesis, including interleukin-1 beta (IL1B), tumor necrosis factor (TNF), chemokine (C-C motif) ligand 2 (ccl2), and chemokine (C-X-C motif) ligand (CXCL). These cytokines play a crucial role in the escalation and continuation of inflammatory processes.. in addition to affecting nuclear factor kappa P pathway activation.[1] By mediating the activation of cytokine production, OPN majorly contributes to the regulation of immune response and coordination of inflammatory processes.[66] The pro-inflammatory mediators triggered by OPN within the synovial membrane diffuse through the synovial fluid and reach the cartilage, resulting in the activation of chondrocytes. This leads to the production of catabolic factors such as proteases and other pro-inflammatory mediators leading to further cartilage damage.[162] OPN's multifaceted role in immune modulation and tissue repair has attracted deserved attention in the field of osteoarthritis research. Osteoarthritis is a condition that affects both the articular cartilage and subchondral bone. It involves the gradual deterioration and thinning of the articular cartilage, leading to a reduction in the flexibility and compliance of the subchondral bone. This disorder is characterized by the breakdown of cartilage, the presence of inflammation, and the experience of pain.[163] Researchers and practicing clinicians recognize the significance of comprehending the role of OPN in the development of osteoarthritis and its potential as a biomarker for disease progression and treatment response. This understanding holds substantial importance in advancing knowledge and improving clinical management of the condition.

Our study aimed to assess the plasma level of OPN before and after six months of total hip replacement in patients with severe primary hip osteoarthritis. We evaluated OPN levels pre- and post-operatively in 30 patients to determine whether or not surgery had an impact on plasma OPN levels. Although we found that OPN post-operatively (mean= 78.5, SD= 37.3

ng/ml) was less than pre-operatively (mean=87.4, SD= 37.4 ng/ml), we found that the difference between OPN plasma levels pre- and post-operatively was not statistically significant (T-test value= -1.2, p-value=0.254).

Published studies on OPN levels in patients suffering from osteoarthritis, albeit scarce, reported different results from ours. For instance, in a study by Abdelnaby et al. [164], They evaluated plasma samples of 14 patients with hip osteoarthritis before and 3 months after hip replacement surgery. They found that the mean plasma OPN pre-operatively was 303.06 ± 64.9 ng/ml. However, they found that plasma OPN levels have increased significantly (p=0.001) after surgery to a mean of 376.14 ± 90.69 ng/ml. OPN levels in Abdelnaby et al. were higher than in our samples. Moreover, they observed a statistically significant increase in OPN levels post-surgery. The differences between our findings and Abdelnaby's may be attributed to sample size and follow-up period. While we took samples from 30 patients before and after 6 months of total hip replacement surgery, Abdelnaby's results come from 14 patients with hip osteoarthritis who were assessed before and after three months of hip replacement. The researchers observed a notable rise in plasma OPN levels following the surgical procedure, which they attributed to the release of OPN from bone, cartilage, or synovium during the operation. Other studies have proposed that the levels of OPN are associated with the extent of articular cartilage damage, suggesting that OPN serves as an early indicator in response to stress signals.[165,166] Another study by Cassuto et al. [167] aimed to assess the role of proinflammatory cytokines, matrix proteins, and bone regulating cytokinesin bone healing of hip arthroplasty patients. They included 24 osteoarthritis patients with one-sided total hip arthroplasty. Surprisingly, they found that inflammatory mediators (CRP, IL-6, OPN) had significantly increased on day one after surgery vs. preoperatively but returned to baseline at six weeks. Abdelnaby et al. [168] conducted a comprehensive search across multiple databases, including Scopus, Web of Science, PubMed, and Embase. The objective of the review was to examine whether plasma OPN could serve as a diagnostic and prognostic factor for evaluating the severity of osteoarthritis.. In their subgroup meta-analysis, they reported that only three studies [169-171] investigated the serum OPN levels in patients suffering from osteoarthritis compared to a control group. The results of the meta-analysis showed that OPN levels were statistically higher in the osteoarthritis group (SMD=3.83, 95% CI=0.23-7.43) compared to controls. They concluded that, these results may suggest that OPN may, indeed, be used as a diagnostic and prognostic marker for osteoarthritis severity. Despite high heterogeneity (I^2 = 99%, $P < 0.00001$) due to variation in OPN measurement kits and their various calibration levels, only Dong et al. [169] had statistically insignificant results (SMD=0.12; 95%CI=0.48-0.71). While their conclusions support the claim that OPN may be used diagnostically and/or prognostically in osteoarthritis patients, our results may suggest otherwise. Many factors may contribute to our results being different including patient variations, the effect of the surgery itself on OPN, or

single relatively short period of follow-up.

5.2. Limitations

The present study was not without limitations. One limitation is the relatively small sample size of 30 patients which may have limited the statistical power to detect small, albeit clinically meaningful, differences in OPN levels pre-and post-operatively. Another limitation of our study is the lack of a control group. Without a proper comparison with a control group of patients who did not undergo hip replacement surgery, it becomes challenging to isolate the specific effect of total hip replacement surgery on OPN levels. Adding a control group will allow for a more comprehensive understanding of the natural course of OPN levels in patients with hip osteoarthritis post-surgery. Additionally, post-operative measurement of OPN was conducted after six months. This time frame is relatively narrow and may not allow us to capture the full spectrum of OPN-level changes that occur during the recovery and healing process. Longer follow-up periods with multiple post-operative assessments may allow a more comprehensive evaluation of the dynamic changes in OPN levels post-surgery.

5.3. Recommendations

Based on the previously mentioned limitations, future studies in this area should consider increasing the sample size to improve the statistical power and generalizability of results. We also encourage future researchers to include a control group of patients who do not undergo the surgery, which will allow a valuable comparison to explore the specific effects of total hip replacement surgery. Furthermore, conducting longitudinal studies with extended follow periods and multiple assessments post-operatively is highly encouraged to allow for a more comprehensive understanding of the temporal changes in plasma OPN levels after surgery. This will provide the full picture of OPN trajectory during recovery and healing and provide insights into the long-term effects of total hip replacement on OPN levels.

5.4. Conclusion

In conclusion, our study assessed the plasma levels of OPN pre- and post-operatively in patients suffering from primary hip osteoarthritis who are undergoing total hip replacement surgery. Although we observed a decrease in OPN levels after 6 months compared to before surgery, the difference was not statistically significant. This suggests that the observed decrease in plasma OPN levels post-operatively may be attributable to random variability or other factors related to surgical intervention. Our novel findings highlight the need for larger studies with control groups and longer follow-up periods to further investigate the effect of total hip replacement surgery on plasma OPN levels. By understanding the dynamics of OPN levels in response to surgery, we might be able to obtain valuable insights into the underlying molecular changes associated with surgical intervention and their clinical implications.

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7. Appendices

7.1. List of Figures

7.2. List of Tables