A COMPARATIVE STUDY OF CLINICAL AND FUNCTIONAL OUTCOME OF OSTEOARTHRITIS OF KNEE JOINT TREATED WITH PLATELET RICH PLASMA VERSUS HYALURONIC ACID INJECTION: A RANDOMIZED CONTROL STUDY

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ABSTRACT

Background and Objectives

OA knee epitomises a significant health burden globally characterized by progressive joint degeneration, pain, and functional limitation. Conservative management approaches include both IA-PRP injection and IA-HA injections emerging as potential therapeutic options. Despite increasing clinical utilization, comparative efficacy data remain limited and inconsistent. This prospective randomized controlled study aimed to evaluate as well as to compare the clinical along with functional outcomes of knee OA treated with PRP versus HA injections, specifically assessing pain reduction and functional improvement across multiple time points to determine optimal therapeutic selection for patients with mild to moderate knee OA.

Methodology

A comparative, prospective, randomized controlled study was conducted at R.L. Jalappa Hospital and Research Centre over an 18-month period, from May 2023 to October 2024. Forty-four patients with mild to moderate knee OA were recruited based on specific inclusion criteria (ages 40-80 years, primary OA, and inadequate response to conservative management) and exclusion criteria (platelet count <150,000/cu.mm, hemoglobin <10 g/dl, uncontrolled diabetes, previous

knee trauma or surgery, and anticoagulant therapy). Participants were randomized into two equal intervention groups (n=22 each) using simple random sampling methodology. A comprehensive clinical assessment was conducted at baseline, with follow-up evaluations performed at 2 weeks, 6 weeks, and 3 months post-intervention. Primary outcome measures included VAS for pain assessment and WOMAC for functional evaluation.

Results

Demographics were comparable between groups with a mean age of 54.23 years (HA) versus 52.41 years (PRP), and similar pain chronicity (7.18 versus 6.82 months). Radiographic assessment revealed identical disease severity distribution with 86.4% patients having Kellgren-Lawrence grade II in both cohorts. Both interventions demonstrated statistically significant improvements from baseline at all assessment timepoints ($p<0.001$). Within the HA group, mean VAS scores progressively decreased from 5.05±0.213 at baseline to 3.73±0.456 at 2 weeks, 3.32±0.568 at 6 weeks, and 2.77±0.612 at 3 months (45.1% reduction). WOMAC scores improved from 69.45±11.484 to 62.64±11.462 (9.8% enhancement). The PRP group exhibited substantially greater improvements, with VAS scores decreasing from 5.14±0.351 to 1.14±0.351 (77.8% reduction) and WOMAC scores improving from 74.68±6.743 to 53.50±6.530 (28.4% enhancement) at 3 months. Comparative analysis revealed progressively divergent efficacy trajectories. By 2 weeks, PRP demonstrated superior pain reduction (mean

difference 0.409, $p=0.006$), with this advantage increasing at 6 weeks (mean difference 1.091, $p<0.001$) and also 3 months (mean diff of 1.636, $p<0.001$). Functional improvements followed similar patterns, with PRP showing superior WOMAC scores at 3 months (mean difference 9.136, $p=0.002$).

Conclusion

This randomized controlled trial provides compelling evidence that while both PRP and HA effectively improve pain and function in mild to moderate knee OA, PRP demonstrates significantly superior clinical outcomes, particularly in medium to long-term assessment periods. The progressive divergence in efficacy trajectories suggests that PRP may facilitate sustained biological effects beyond the initial intervention, supporting its preferential utilization in clinical practice, especially when durable symptomatic relief and functional improvement are primary therapeutic objectives.

Keywords: Osteoarthritis, Knee, Platelet-Rich Plasma, Hyaluronic Acid, Intra-articular Injections, WOMAC Score

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ABBREVIATIONS

Abbreviation	Explanation
OA	Osteoarthritis
PRP	Platelet-Rich Plasma
HA	Hyaluronic Acid
MCL	Medial Collateral Ligament
LCL	Lateral Collateral Ligament
ACL	Anterior Collateral Ligament
PCL	Posterior Collateral Ligament
MMPs	Matrix Metalloproteinases
TNF-α	Tumour Necrosis Factor-Alpha
IL-1β	Interleukin-1β
KL	Kellgren And Lawrence
KOGS	Knee Osteoarthritis Grading System
PDGF	Platelet-Derived Growth Factor
VEGF	Vascular Endothelial Growth Factor
IGF-1	Insulin-Like Growth Factor-1
BMI	Body Mass Index
VAS	Visual Analogue Scale

WOMAC	Western Ontario and Mcmaster Universities Osteoarthritis Index
SF 36	Short Form Health Survey Questionnaire - 36
IKDC	International Knee Documentation Committee
PRGF	Plasma Rich In Growth Factors
HSS	Harris Hip Score
MRI	Magnetic Resonance Imaging

INTRODUCTION

OA stands as the most prevalent chronic degenerative joint disorder and a leading cause of disability globally, affecting approximately 303 million individuals globaly.[1,2] Primarily characterized by progressive articular cartilage deterioration, the disease encompasses broader joint pathology including subchondral bone refashioning, osteophyte development, inflamed synovium, and ligamentous laxity.[3,4] Knee OA presents particularly challenging management dilemmas due to its high occurrence, progressive nature, and significant impact on patient QOL.

The pathophysiology of OA involves complex, multifactorial mechanisms beyond mere "wear and tear." Contemporary understanding recognizes OA as an active biological process involving inflammatory mediators, cellular responses to mechanical stress, and aberrant tissue repair mechanisms.[4] This evolving perspective has driven exploration of novel therapeutic interventions targeting these biological pathways, particularly for patients with mild to moderate disease where conservative management proves inadequate yet surgical intervention remains premature.[3]

Conventional management strategies for knee OA include weight reduction, physical therapy, activity modification, analgesics, and non-steroidal anti-inflammatory drugs. However, these approaches frequently provide inadequate symptomatic relief and fail to address underlying disease mechanisms.[5,6] This therapeutic gap has stimulated interest in intra-articular injections as a minimally invasive intermediate intervention, with corticosteroids, HA, and more recently, autologous PRP emerging as prominent options.[7,8]

HAs are available in synovial fluid and cartilage matrix, has been utilized as a visco-supplementation therapy for over two decades. HA injections purportedly enhance joint lubrication, reduce inflammatory cytokine production, and potentially stimulate endogenous hyaluronan synthesis.[9,10]Clinical studies have demonstrated variable efficacy in decreasing pain along with promoting function in knee OA patients, with benefit durations typically ranging from 6 to 12 months.[11,12]

PRP represents a more recent biological intervention derived from autologous blood processing to concentrate platelets and associated growth factors. PRP's therapeutic potential stems from its rich content of growth factors, including PDGF, TGF-β, VEGF, and IGF-1.[13,14] These bioactive molecules potentially modulate inflammation, stimulate mesenchymal stem cell proliferation, enhance chondrocyte function, and promote extracellular matrix synthesis.[15,16]

The comparative efficacy of IA-PRP versus IA-HA has been the subject of significant research interest over the past decade. Multiple RCTs have investigated their relative merits. [5,6,8,17]A systematic review by Belk et al. encompassing 18 randomized controlled trials demonstrated superior pain reduction along with functional advancement with IA-PRP compared to IA-HA across multiple timepoints up to I year.[17] Similarly, Tang et al. conducted a meta-analysis of 14 RCTs showing significantly better outcomes with IA-PRP than IA-HA.[18]

The landmark 5-year double-blind randomized controlled trial by Di Martino et al. provided valuable long-term comparative data, demonstrating PRP superiority at 2 years, though this advantage diminished by 5-year follow-up.[19] Several studies have also investigated the potential synergistic effects of combining PRP and HA, with meta-analyses by Zhao et al. and Zhang et al. suggesting enhanced therapeutic efficacy with combination therapy compared to HA monotherapy.[20,21]

Despite the growing evidence that supports IA-PRP's efficacy, significant heterogeneity exists regarding preparation methods, administration protocols, patient selection criteria, as well as outcome measures. Additionally, the optimal treatment approach may vary based on patient-specific factors including age, BMI, and disease severity of OA knee. Particularly addressing treatment choices for overweight as well as obese patients, Luo et al. advised PRP as the recommended choice in this demographic.[22]

This RCT is to evaluate, in patients with mild to moderate knee OA, the clinical as well as functional results of IA-PRP vs IA-HA injections, therefore augmenting the evidence base guiding therapeutic decision-making for this prevalent but difficult disease.

OBJECTIVES

1. To study the clinical as well as functional outcomes of OA of knee joint treated with IA-PRP.
2. To study the clinical as well as functional outcomes of OA of knee joint treated with IA-HA injection.
3. To compare the clinical as well as functional outcome of OA of knee joint treated with IA-PRP vs IA-HA.

REVIEW OF LITERATURE

Anatomy[23]

The knee joint represents one of the body's most complex articular structures, functioning as a modified hinge joint. Anatomically, the knee comprises three functional compartments: the patellofemoral joint and the medial and lateral tibiofemoral articulations. The distal femur presents two condyles that articulate with the proximal tibial plateau, creating an inherently incongruent interface that requires specialized stabilizing structures.

The joint is enveloped by a fibrous capsule, reinforced anteriorly by the quadriceps tendon and patella, which continues as the patellar ligament to insert on the tibial tuberosity. Collateral ligaments provide critical medial and lateral stability: the MCL as a broad, flat structure, and the LCL as a cord-like band. ACL and PCL—function as central pivots controlling anteroposterior translation and rotational movements.

The menisci, fibrocartilaginous semilunar structures, enhance joint congruency, distribute loads, and absorb shock. The synergy between dynamic muscular forces (quadriceps, hamstrings, gastrocnemius) and passive restraints maintains optimal joint mechanics. The synovial membrane produces synovial fluid that provides nutrition and lubrication to articular surfaces. This integrated system allows the knee to withstand forces exceeding four times body weight during routine activities while maintaining remarkable stability and mobility.

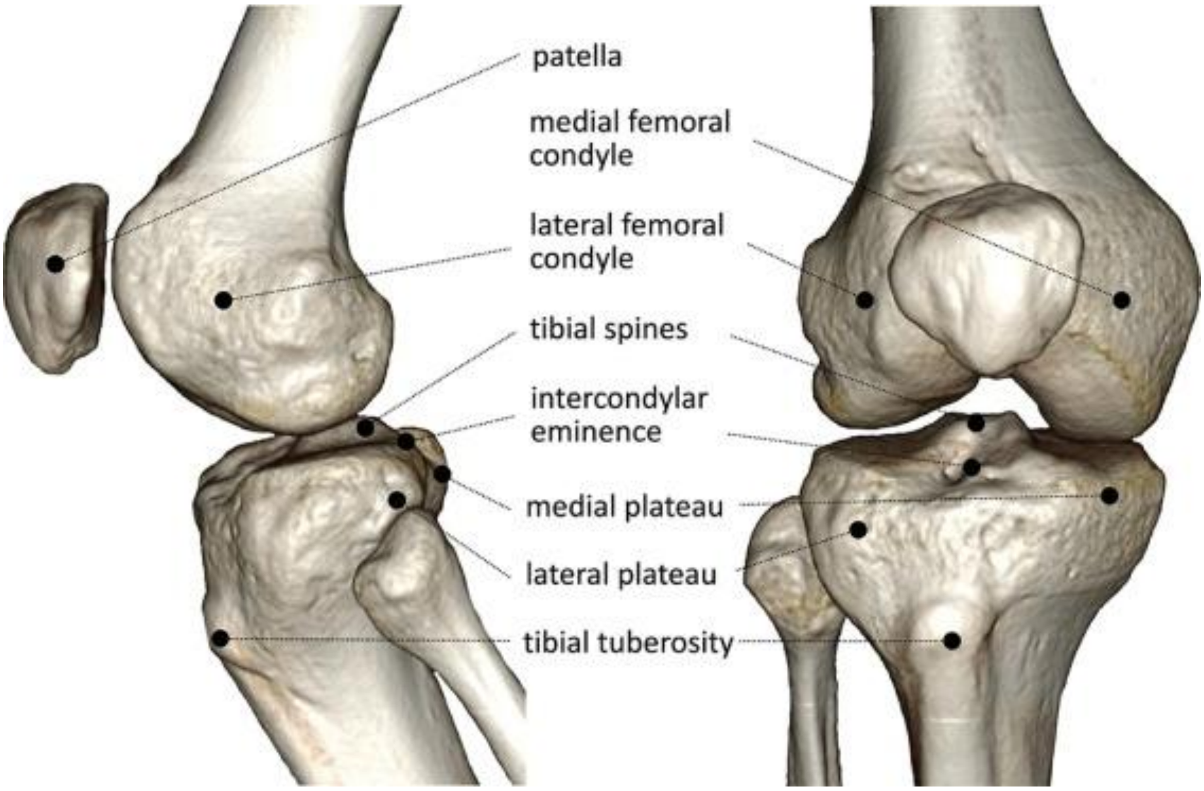

Figure 1: Anatomy of the knee[24]

Knee OA

OA mostly impacts the diarthrodial joints and is linked to an escalating financial burden as a result of an aging population.[25]These are classified into 2 categories: primary OA and secondary OA. Classically, OA presents with joint pain and loss of function; however, clinically, the disease can range from being an innocuous incidental finding to a debilitating and life-altering condition.[1]

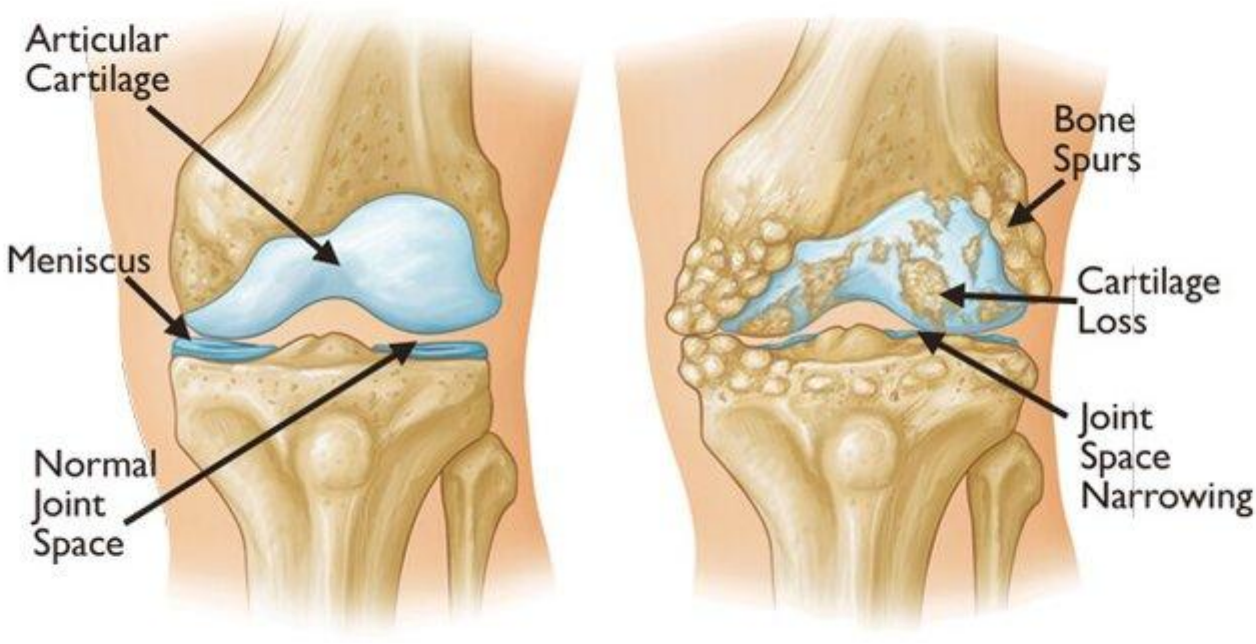

Figure 2: Normal knee and OA Knee.[26]

Burden of Knee OA at Global Level

Knee OA is quickly becoming the top cause of impairment in the elderly, and OA as a whole makes up one of the most common chronic joint illnesses in the world. The global burden of knee OA has escalated significantly, affecting approximately 303 million people worldwide.[11] This increasing prevalence correlates with worldwide demographic transitions toward aging populations and rising obesity rates. According to Courties et al. (2024), knee OA accounts for more disability than any other joint condition, with substantial socioeconomic implications through healthcare utilization, reduced workforce productivity, and diminished quality of life. The economic burden encompasses both direct medical costs as well as indirect costs from lost efficiency, anticipated to exceed $136.8 billion annually in the United States alone.[2]

Burden at national level

Given cultural traditions including repeated kneeling as well as crouching, which can hasten joint degeneration, knee OA is a major disability in the Indian setting. Although the epidemiological data in India is still lacking, studies indicate rates of between 22-39% among individuals over 40 years, with greater rates are observed in rural communities than in metropolitan areas.[3]The burden is compounded by delayed healthcare seeking behaviour, limited access to specialized care in rural regions, and high out-of-pocket expenditure for treatments. Furthermore, the economic impact extends beyond direct healthcare costs to include family caregiving burden and lost wages, creating substantial socioeconomic strain. These factors collectively contribute to knee OA representing a significant public health challenge in India, necessitating targeted interventions and cost-effective treatment strategies such as intra-articular therapies.[4]

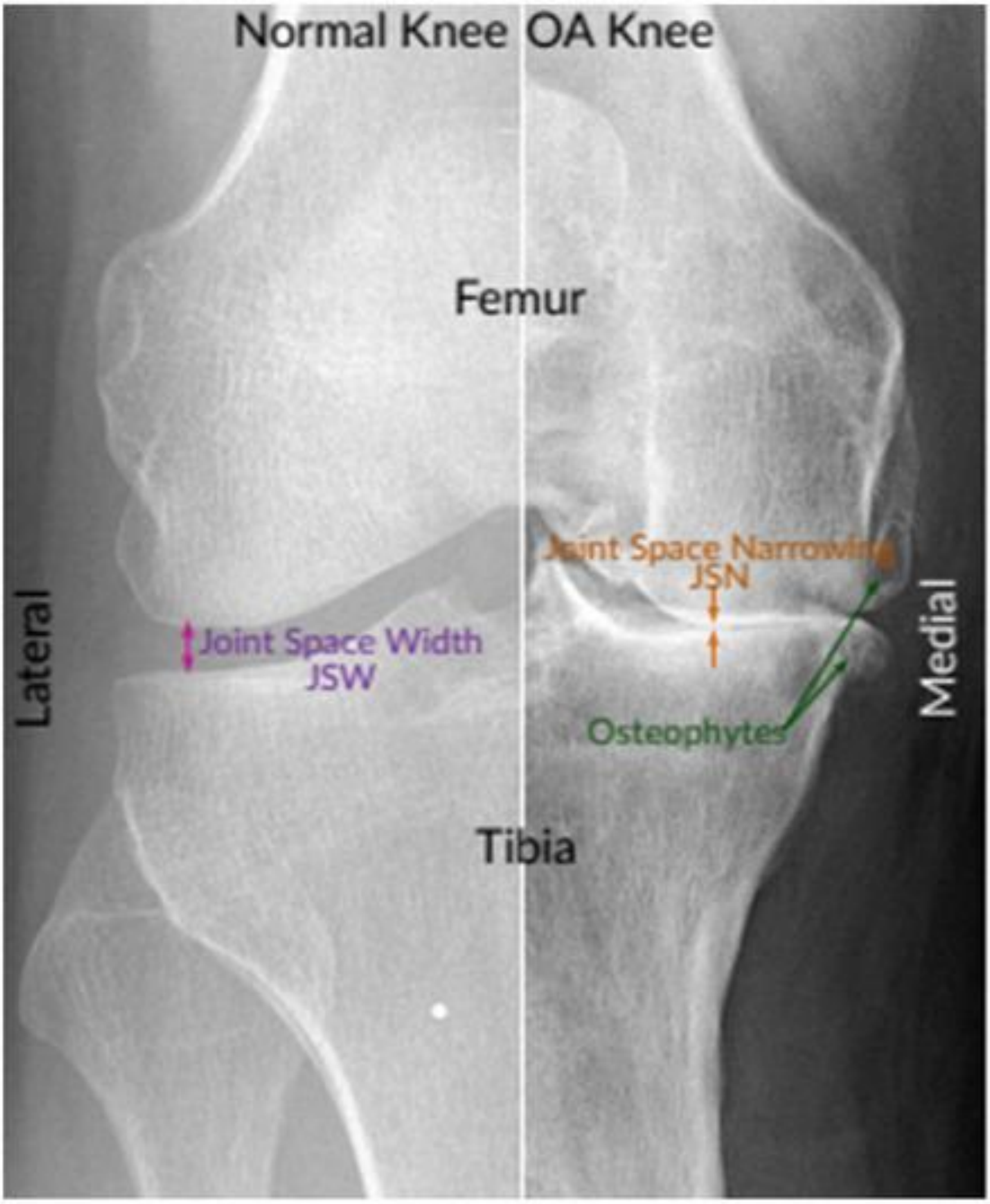

Figure 3: X-ray picture of normal and OA knee.[27]

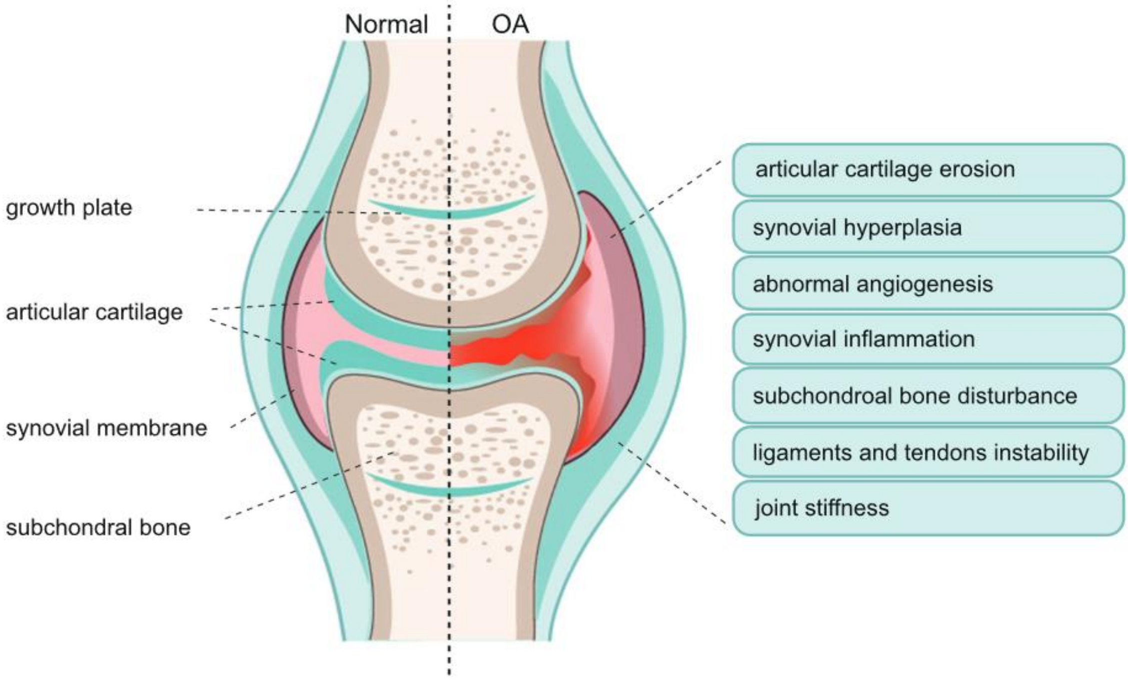

Figure 4: Phenotypes of OA[28]

Pathophysiology of Knee OA

Cartilage Degradation

Arthritis develops when chondrocytes, the cells in charge of cartilage maintenance, experience a disparity between their anabolic as well as catabolic processes, leading to the breakdown of articular cartilage in Knee. Cartilage degradation is driven by the overexpression of MMPs and aggrecanases, which break down the ECM components such as collagen and aggrecan.[29] The mechanical stress on the knee joint exacerbates this process, as it leads to the release of pro-inflammatory cytokines and ROS that further accelerate cartilage breakdown.[30]

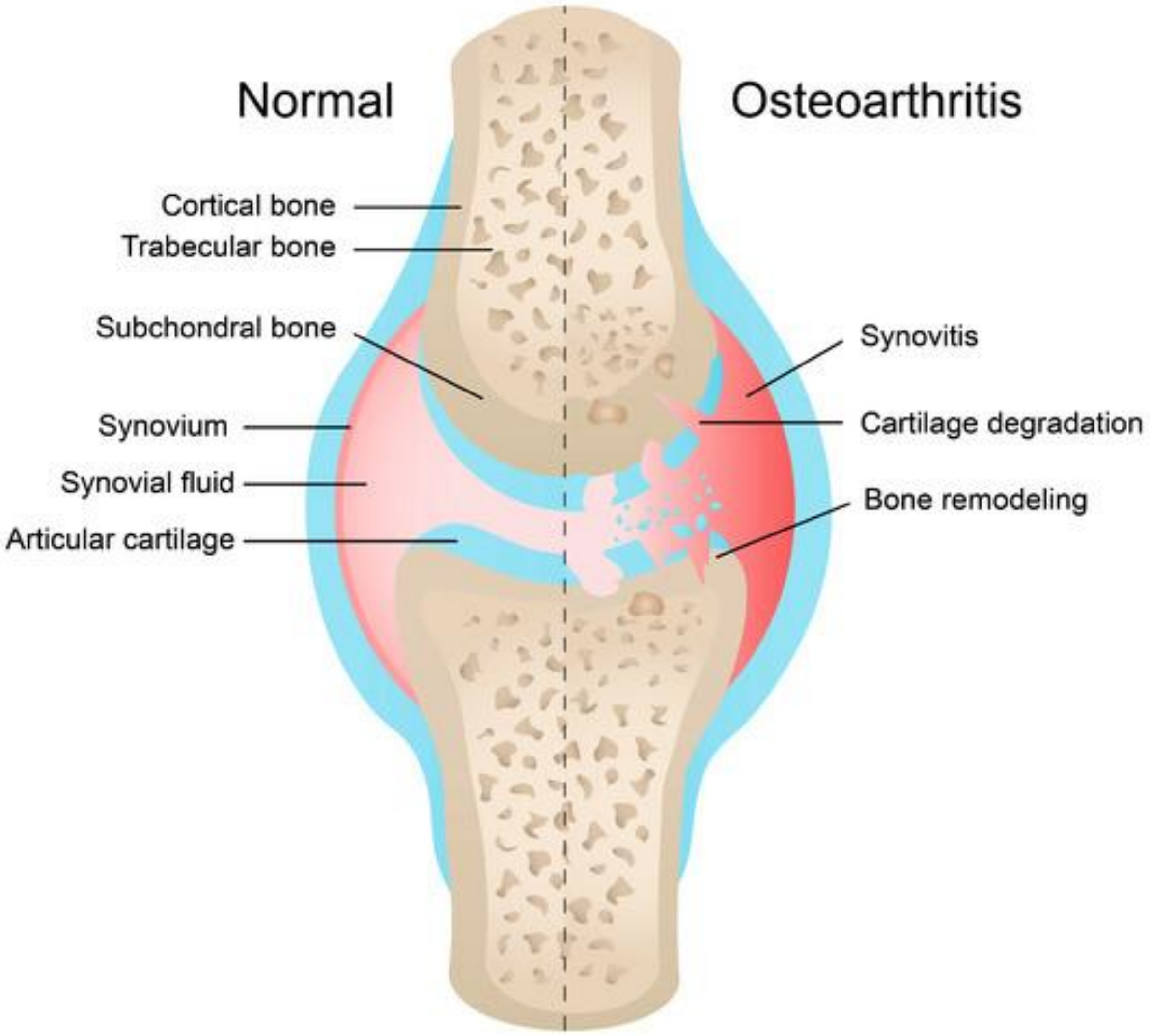

Figure 5: Bone and joint health depicted schematically. Cartilage degeneration is a hallmark of OA. [31]

Inflammatory Processes

Though less than in RA, inflammation is a major factor in the onset of OA Knee. Synovial inflammatory processes, also referred to as synovitis, include immune cells invading the synovial membrane along with elevated levels of mediators of inflammation like IL-1β as well as TNF-α.[32]These mediators help to sensitize nociceptors as well as degrade cartilage, therefore causing pain along with joint stiffness. Synovitis has been associated with the development of structural abnormalities in the knee joint and a predictor of pain degree and functional impairment.[33]

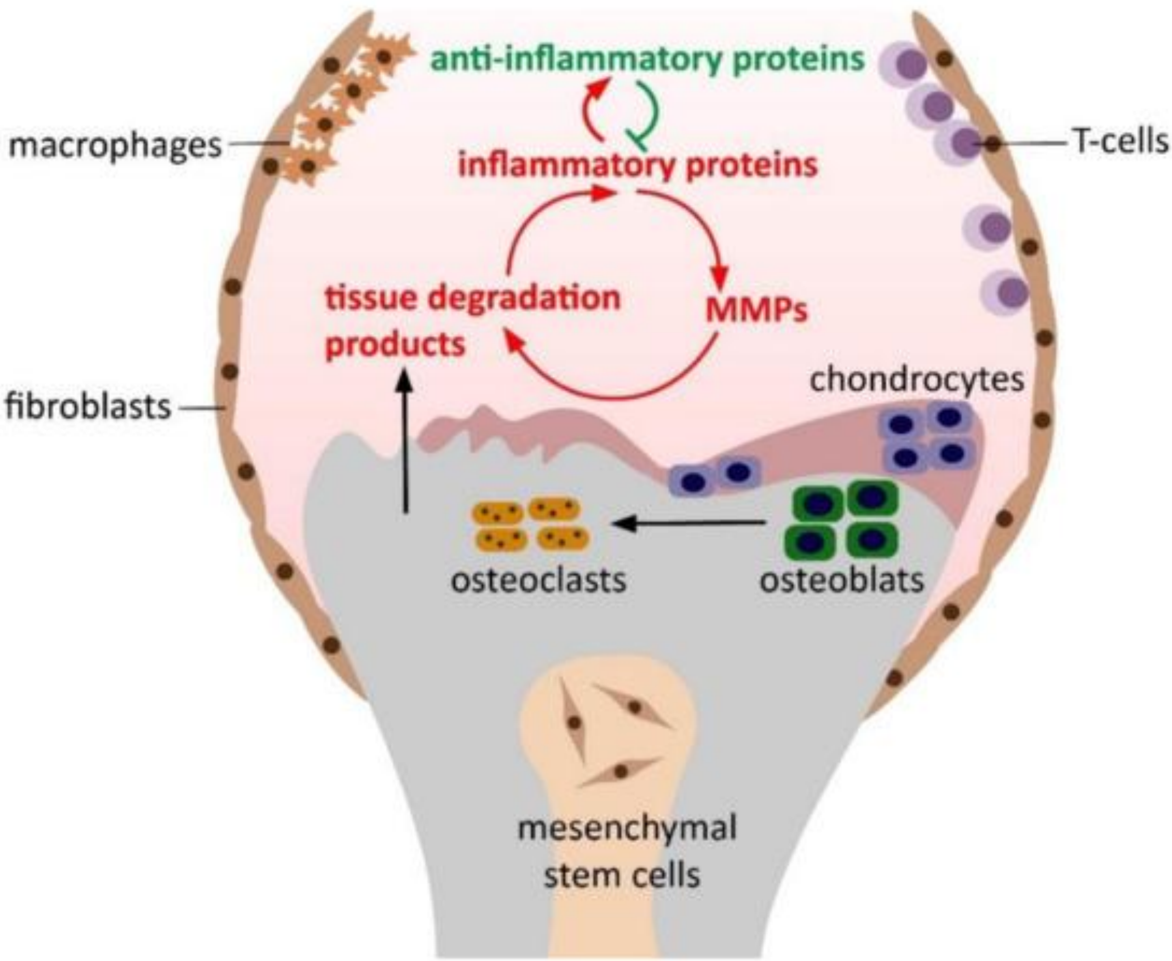

Figure 6: Pathogenesis of OA[34]

Role of Synovial Fluid

Synovial fluid nourishes the avascular cartilage and alters OA significantly. Synovial fluid's makeup changes; more inflammatory cytokines and catabolic enzymes that hasten cartilage destruction are present.[35]Key component of synovial fluid, HA loses viscoelastic qualities, therefore affecting joint lubrication and shock absorption. This aggravates OA symptoms and helps to explain the mechanical wear and tear on the joint surfaces.[36]

Variations in subchondral bone

Two structural changes that subchondral bone endures in OA include sclerosis and the formation of osteophytes. These modifications are supposed to be the reaction of changed joint biomechanics and higher mechanical stresses. Subchondral bone sclerosis results in increased bone stiffness, which may exacerbate cartilage damage by altering the distribution of mechanical forces across the joint. Osteophytes, or bone spurs, develop at the joint margins and are a characteristic feature of OA, contributing to joint pain and reduced mobility.

Biomechanical Factors

Biomechanical factors, including joint instability and malalignment, play a critical role in the initiation and progression of knee OA. Abnormal joint loading due to obesity, previous joint injuries, or anatomical deformities can lead to uneven distribution of forces, accelerating cartilage wear and joint degeneration.[37]

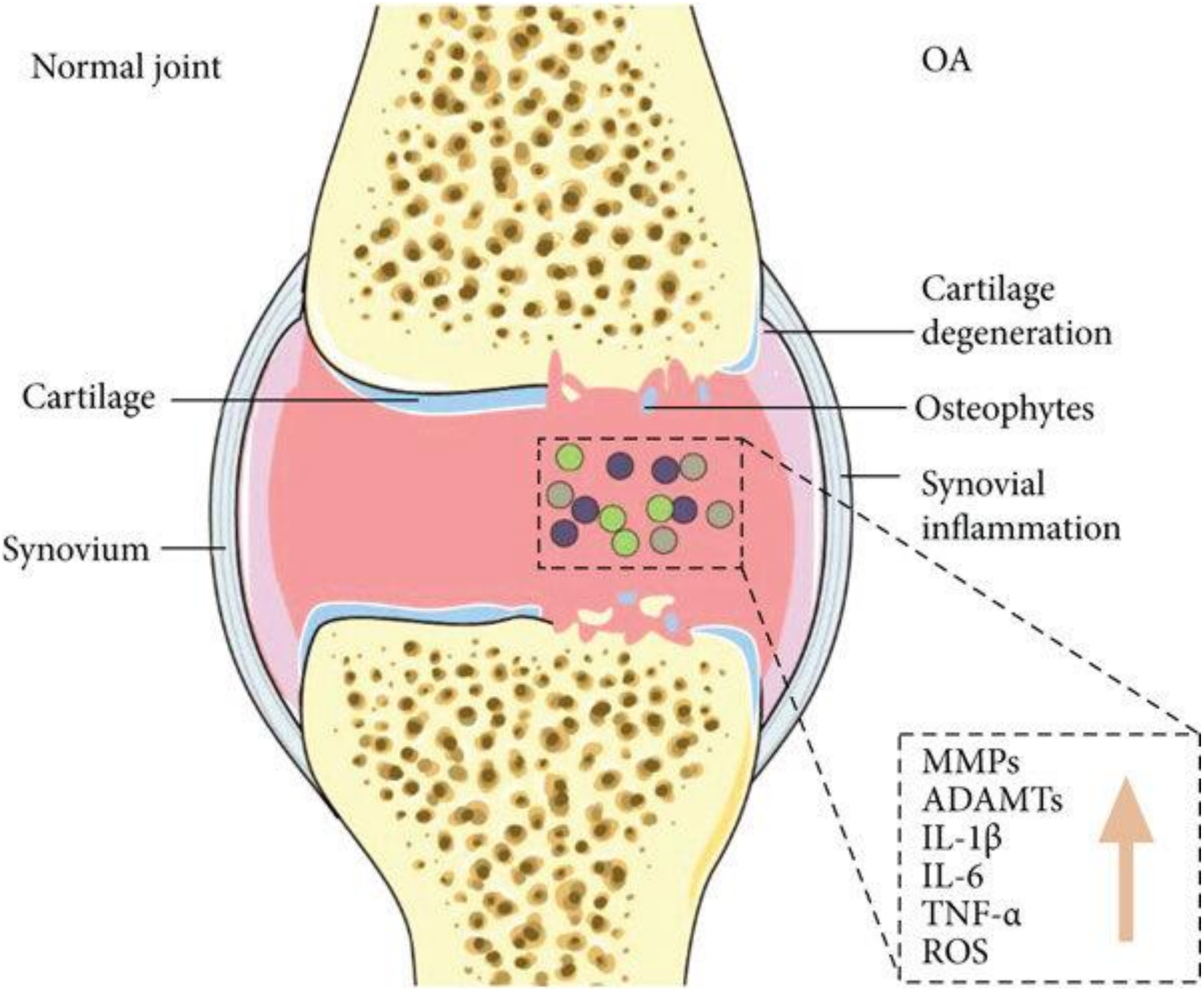

Figure 7: Diagram of normal and cartilage OA joints.[38]

Osteophyte formation

It is a common feature of OA in the knee. These bony outgrowths develop as a result of the body's attempt to repair cartilage damage within the joint. Osteophytes, or bone spurs, occur along the edges of the bone and are often visible in radiographic images of the knee. Their formation is influenced by factors including mechanical stress and the biological processes that govern cartilage repair.[39] In OA, the knee experiences wear and tear, leading to cartilage breakdown. As the cartilage deteriorates, the bones in the joint may rub against each other, causing pain and further damage. The body responds by creating osteophytes as a stabilizing mechanism, though these spurs can contribute to joint stiffness and discomfort. The presence of osteophytes is often used as a diagnostic criterion in OA.[40] Osteophytes can be an early indicator of OA progression. Their size and direction may vary, and their development can precede visible joint space narrowing, making them a potential biomarker for early OA detection. Understanding the role of osteophytes in knee OA is crucial for developing targeted treatments to alleviate symptoms and slow disease progression.[41]

Risk Factors

Knee OA aetiology involves complex interactions between systemic and local factors. Age represents the most consistent risk factor, with prevalence rates increasing dramatically after 50 years, reflecting cumulative exposure to various determinants as well as age-related changes in chondrocyte function and matrix composition.[11] Female gender confers increased susceptibility, particularly post-menopause, suggesting hormonal influences on cartilage metabolism and joint integrity. Obesity significantly amplifies risk through mechanical loading and metabolic pathways, with each unit rise in BMI associated with 11% mounted risk of knee OA development.[3]

Genetic predisposition accounts for approximately 30-65% of OA heritability, with specific polymorphisms affecting structural proteins and inflammatory mediators implicated in disease susceptibility.[4] Previous joint trauma, particularly anterior cruciate ligament and meniscal injuries, substantially increases subsequent OA risk through altered biomechanics and inflammatory cascades. Occupational factors including repetitive joint loading, kneeling, and squatting contribute significantly, particularly in agricultural and construction sectors. Anatomical variations such as varus/valgus malalignment and leg length discrepancies create abnormal joint stresses that accelerate cartilage degradation.

Metabolic syndrome components correlate with both OA incidence and progression, suggesting shared inflammatory pathways beyond mechanical factors.[2] Nutritional deficiencies, particularly vitamin D, may influence cartilage metabolism and subchondral bone quality. Cigarette smoking demonstrates conflicting associations, potentially offering modest protection through altered inflammatory pathways despite overall detrimental health effects. Understanding these multifactorial risk factors facilitates targeted preventive strategies and optimization of treatment approaches for specific patient populations.[3]

Complications

Knee OA complications extend far beyond the cardinal symptoms of pain and stiffness, encompassing a cascade of physical, psychological, and functional sequelae. Progressive joint deformity represents a significant complication, with varus (bow-legged) deformity predominating in medial compartment disease and valgus (knock-kneed) deformity in lateral compartment involvement. These malalignments further exacerbate mechanical stress, creating a detrimental cycle of accelerated cartilage degeneration and worsening symptomatology.[3] Muscle weakness, particularly involving the quadriceps, develops through disuse atrophy and neurological inhibition mechanisms, compromising joint stability and further impairing function.

Joint instability emerges as both a complication and contributor to disease progression, increasing fall risk and associated morbidity. Osteophyte formation may impinge surrounding tissues, causing mechanical symptoms and potentially diminishing range of motion. Advanced cases may develop subchondral bone cysts and bone marrow lesions that serve as additional pain generators resistant to conventional analgesics.[2] Beyond physical manifestations, knee OA significantly impacts psychosocial wellbeing, with approximately 30-50% of patients developing clinical depression or anxiety, often underdiagnosed and undertreated.

Functional limitations progressively impair activities of daily living, with approximately 25% of knee OA patients eventually developing significant disability requiring assistive devices or personal assistance.[1] Disturbed sleep architecture from nocturnal pain contributes to daytime fatigue and diminished cognitive function. Analgesic complications represent iatrogenic challenges, with

NSAID-associated gastrointestinal bleeding and opioid dependence concerns. Ultimately, these multidimensional complications underscore the importance of early intervention with disease-modifying therapies such as PRP and HA that might delay disease progression and preserve function through biological mechanisms rather than merely addressing symptoms.[3]

Classifications

The use of plain radiography to diagnose OA is still prevalent. According to KL's 1957 description, the initial organized efforts to create a radiographic categorization system for OA were[42]

The KL classification was originally described using AP knee radiographs. A rating from 0 to 4 was given to each radiograph, with 0 indicating no OA and 4 indicating severe OA, to indicate the growing severity of the condition.[43]

The Ahlbäck classification system for knee OA categorizes the severity of the condition based on radiographic findings, specifically focusing on joint space narrowing and bone attrition, with grades ranging from 1 to 5.

Figure 8: KL scale[44]

In order to help surgeons decide on the best type and period for knee arthroplasty, the KOGS was created as a radiological grading system for destructive knee arthritis. It is exhaustive, simple to use, and able to assess all three compartments of the knee.[45]

However, there is a lack of objectivity and agreement across observers when using more conventional radiography grading methods like the KL system. This is mainly because there are restrictions and discrepancies in the ways that diseases are evaluated and the degrees of technical expertise used. As a consequence, there is a lack of consistency in the treatment plans that patients get. In order to properly assess knee OA, quantitative evaluation techniques for imaging of the knee joint are urgently required.

Grade	KL Scale	Ahlbäck Classification	KOGS
Grade 0	No pathological features of osteoarthritis (OA)		
Grade 1	Suspicious narrowing of the joint space and possible osseous lip	Joint space narrowing, with or without subchondral sclerosis. Joint space narrowing is defined by this system as a joint space <3 mm, or less than half of the space in the other compartment, or less than half of the space of the homologous compartment of the other knee	An isolated medial, lateral tibiofemoral, or patella-femoral joint OA with ligament stability and two functionally intact compartments
Grade 2	Clear bone tissue and possible stenosis of the joint space	Obliteration of the joint space	Deteriorating isolated lesion with ligament stability and a correctible coronal subluxation
Grade 3	Moderate multiple bone tissue, clear narrowing of the joint space, slight sclerosis, and possible deformity of the ends of the bones	Bone defect/loss < 5 mm	Includes an isolated medial or lateral tibiofemoral OA and concomitant pathologies such as anterior cruciate ligament deficiency (3A) or grooving of patella-femoral joint or patellectomy (3B)
Grade 4	Large bone tissue, marked narrowing of the joint space, severe sclerosis, and clear deformities of the ends of the bones	Bone defect/loss between 5 mm and 10 mm	Includes cases of bi-compartmental tibiofemoral OA without concomitant ligament instability (4A) and with ligament instability (4B)
Grade 5		Bone defect/loss >10 mm, often with subluxation and arthritis of the other compartment	

Table 1: Comparison of KL scale, Ahlbäck classification, and KOGS[44]

PRP

PRP's regenerating properties have made it a top contender as a treatment for osteoarthritis (OA) of the knee. This section delves into the workings of PRP, including its biological make-up, preparation techniques, and the function of growth factors and bioactive compounds.

Mechanism of Action

PRP exerts its therapeutic effects primarily through the modulation of inflammation and promotion of tissue regeneration. It is known to reduce the concentration of cytokines such as IL-1β and in the synovial fluid, thereby alleviating inflammation and pain associated with OA.[46] Additionally, PRP enhances the synthesis of cartilage matrix components, such as collagen along with proteoglycans, by stimulating chondrocyte proliferation and differentiation.[47] The sustained release of bioactive molecules from PRP also facilitates the repair of damaged cartilage and inhibits further degeneration.

Biological Composition and Preparation Methods

PRP is derived from autologous blood, which is processed to concentrate platelets above baseline levels. The preparation of PRP involves centrifugation to separate the plasma from red blood cells, followed by a secondary spin to concentrate platelets. [48]

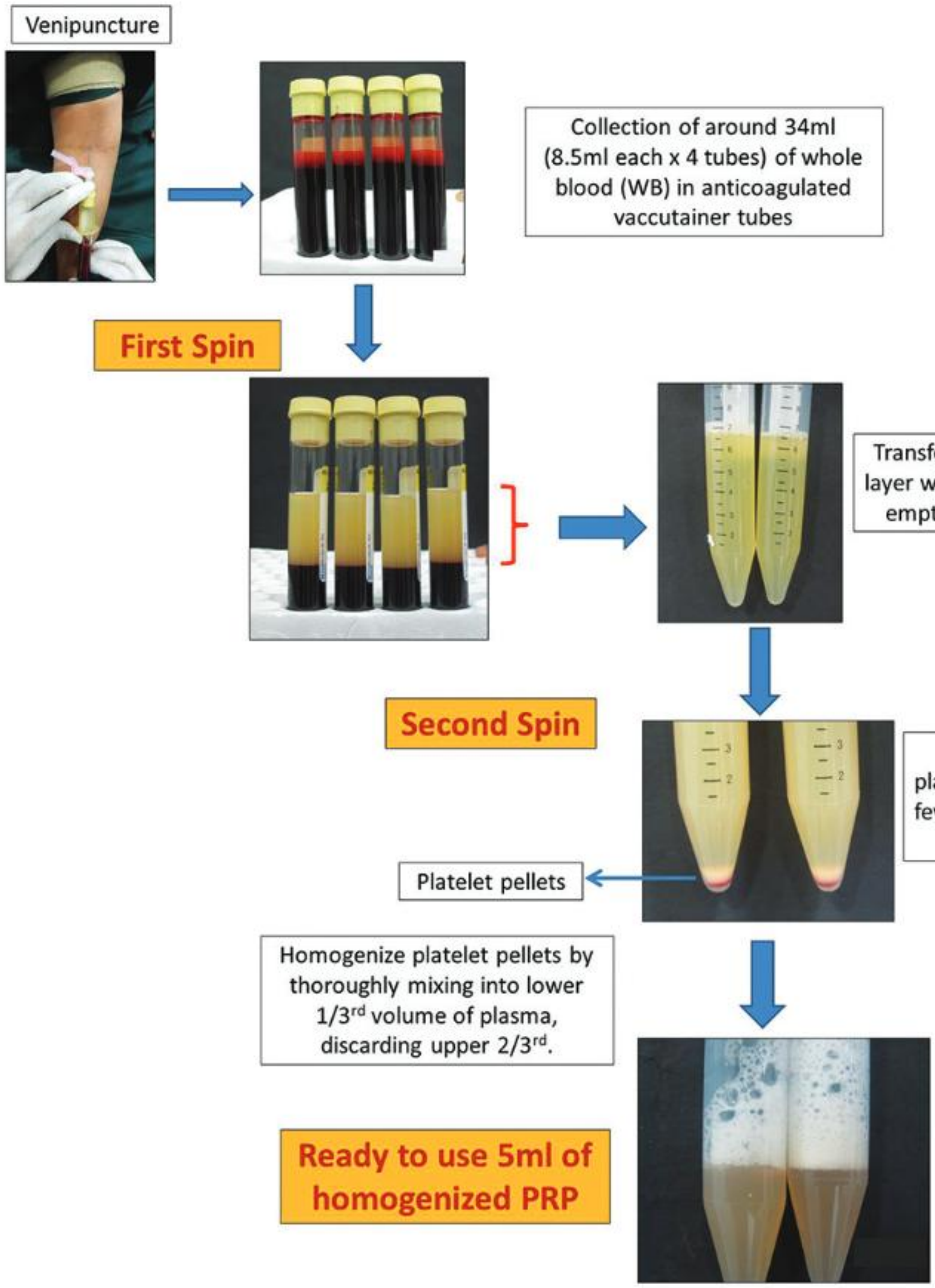

Figure 9: Flowchart describing preparation of PRP[49]

Platelet Growth Factor Type	Growth factor Source	Biological Actions
Platelet derived growth factor (a-b)	Platelets, osteoblasts, endothelial cells, macrophages, monocytes, smooth muscle cells	Mitogenic for mesenchymal celss and osteoblasts, stimulates chemotaxis and mitogenesis in fibroblast/glial/smooth muscle cells, regulates collagenase secretion and collagen synthesis, stimulate macrophage and neutrophil chemotaxis
Transforming growth factor TGF(alpha –beta)	Platelets, extracellular matrix of bone, cartilage matrix, activated TH1 cells and natural killer cells, macrophages/monocytes and neutrophils	Stimulates undifferented mesenchymal cell proliferation ; regulates endothelial, fibroblastic and osteoblastic mitogenesis ; regulates collagen synthesis and collagenase secretion, regulates mitogenic effects of growth factors, stimulate endothelial chemotaxix and angiogenesis, inhibits macrophage and lymphocyte proliferation
Vascular endothelial growth factor, VEGF	Platelets, endothelial cells	Increases angiogenesis and vessel permeability, stimulates mitogenesis for endothelial cells
Epidermal growth factor, EGF	Platelets, macrophages, monocytes	Stimulates endothelial chemotaxis / angiogenesis, regulates collagenase secretion, stimulates epithelial /mesenchymal mitogenesis
Fibroblast growth factor, FGF	Platelets, macrophages, mesenchymal cells, chondrocytes, osteoblasts	Promotes growth and differentiation of chondrocytes and osteoblasts, mitogenic for mesenchymal cells, chondrocytes and osteoblasts
Connective tissue growth factor CTGF	Platelets through endocytosis from extracellular environment in bone marrow	Promotes angiogenesis, cartilage regeneration, fibrosis and platelet adhesion
Insulin like growth factor – 1 IGF -1	Plasma, epithelial cells, endothelial cells, fibroblasts, smooth muscle cells, osteoblasts, bone matrix	Chemotaxis for fibroblasts and stimulates protein synthesis. enchances bone formation by proliferation and differentiation of osteoblasts

Table 2: Platelet growth factors in PRP and their specific characteristics[49]

Venipuncture

The initial phase in PRP procurement involves peripheral blood collection through standardized venipuncture techniques. As delineated by Mazzocca et al. (2012), venous blood withdrawal is typically performed using a large-bore needle (18-21 gauge) with a slow-draw technique to minimize platelet activation during collection.[48] Dhurat and Sukesh (2014) emphasized that anticoagulation with acid-citrate-dextrose (ACD-A) is preferred over heparin or EDTA to preserve platelet functionality.[49] A critical volume of 20-60 mL of autologous blood is routinely collected, based on the anticipated concentration factor and final volume requirements.[50]

Preparation of PRP

The preparation methodology significantly influences PRP composition and bioactivity. According to Cavallo et al. (2016), a two-step centrifugation protocol yields optimal platelet concentration: an initial low-speed centrifugation (230g for 10 minutes) separates erythrocytes from the plasma component, followed by a high-speed centrifugation to concentrate platelets.[51] Sundman et al. (2014) demonstrated that leukocyte content modulates the inflammatory profile, whereas Y and U (2018) emphasized that activation methods—including calcium chloride, thrombin, or mechanical activation—significantly affect growth factor release kinetics and concentrations of IL-1β, TGF-β, and PDGF.[46]

Dose of Injection in OA Knee

Rodríguez-Merchán (2022) synthesized clinical evidence supporting intra-articular PRP injections at volumes of 3-8 mL per administration in osteoarthritic knees. The optimal therapeutic regimen consists of 2-3 injections at 2-4 week intervals, with platelet concentrations ranging from 2.5-5 times baseline levels.[47] Wu et al. (2011) correlated clinical efficacy with platelet concentrations of 1.0-1.5×10^6 platelets/μL.[52]El-Sharkawy et al. (2007) and Pavlovic et al. (2016) demonstrated that therapeutic benefits derive from the synergistic effects of various growth factors, particularly TGF-β1, PDGF, and IGF-1, which mediate chondroprotective and anti-inflammatory mechanisms through modulation of synovial cytokine profiles.[53]

Growth Factors and Bioactive Molecules

PRP is rich in growth factors and bioactive molecules that are crucial for its regenerative properties. Key growth factors present in PRP include PDGF, TGF-β, VEGF, and IGF-1.[51]These elements are critical for regenerating damaged tissues because they stimulate angiogenesis, cell proliferation, and matrix production. Furthermore included in PRP are cytokines and chemokines that control the inflammatory response and boost anti-inflammatory action of the treatment.[54]

The release of these bioactive molecules depends on the activation technique of PRP, therefore influencing the whole therapeutic result. Two activators who could induce platelets to degranulate and release growth factors are calcium chloride and thrombin.[55]

Anti-inflammatory and Regenerative Properties

The strong anti-inflammatory along with regeneration properties of PRP are well-known; its main mediation is via the high concentration of growth factors as well as cytokines it contains. Promoting tissue healing along with controlling inflammation depend critically on these bioactive chemicals. By lowering cytokine levels including TNF-α plus IL-1β, PRP helps to ease OA's inflammation as well as discomfort.[53] By encouraging chondrocyte proliferation along with differentiation—which helps cartilage regeneration—PRP also improves the production of ECM components like collagen as well as proteoglycans. These qualities make PRP a desirable choice for OA management as they might help to lower symptoms and slow down the spread of diseases.[52]

Standardization Challenges in Preparation Protocols

The therapeutic potential of IA-PRP is hindered by the challenges in standardizing its production methods, which prevents its clinical application. Although platelet activation techniques, centrifugation procedures, along with anticoagulant use may all have a significant impact on PRP components as well as effectiveness, it is important to note that autologous blood is spun to concentrate platelets for PRP formation. Consistent treatment protocols along with comparison of study results are made more difficult by these variations in PRP preparation. [50]

To guarantee constant PRP quality as well as effectiveness, standardized procedures are necessary before treatment (Menchisheva and Mirzakulova, 2018). Clinical usage of IA-PRP is already complicated because to the lack of agreement on the best platelet concentration, activation technique, as well as volume to utilize. If we want PRP to reach its full therapeutic potential as well as to become widely used in clinical practice, we must solve these standardization difficulties before injection.[56]

HA

HA is an important part of treatments used to manage OA in the knee. It works because it has special properties and ways of working that target the main changes that are causing the problem in the joint.

Mechanism of Action

Visco-supplementation is the main way that HA helps people with OA. By injecting IA-HA directly into the knee, the amounts of natural HA rise, which restores the gelatinous properties of the synovial fluid in the joint.[57] This makes the joints more flexible as well as able to handle stress, which reduces pain along with it improves joint function. In addition, HA works with cell surface receptors like CD44 to help make collagen as well as proteoglycans, two important substances for knee joint health.[58]

Physical Function in Synovial Fluid

HA is a main part of synovial fluid in a healthy knee joint, which helps explain why it is both thick along with stretchy nature. A shock absorber protects the joint from mechanical stress, and a lube makes it possible for the articular surfaces to move smoothly together. In OA knee, the quantity as well as molecular weight of HA are much smaller, which makes these functions less effective along with it makes joint pain and decline worse.[59]

Viscoelastic Properties and Joint Lubrication

The way HA lubricates joints depends much on its flexible nature. HA exhibits "shear-thinning," which is the property whereby its viscosity falls under shear stress. For moving joints, this makes it a suitable lubricant. Maintaining joint cartilage from wear and friction is mostly dependent on this ability, which also slows down OA development.[60]

Anti-inflammatory Effects

HA's anti-inflammatory properties also enable it to be a therapy for OA. It inhibits the entrance of inflammatory cells into the synovium, therefore lowering inflammation and the accompanying discomfort; it also blocks the synthesis of cytokines causing inflammation.[61] Higher molecular weight forms of HA have more anti-inflammatory properties, which aid for a longer period.[62]

Different Formulations and Molecular Weights

Different molecular weights as well as compositions of HA affect their therapeutic effectiveness in OA knee treatment. Higher molecular weight in HA usually has superior viscoelastic characteristics as well as longer residence duration in the joint, thereby offering extended symptom alleviation in severe cases.[63] Various formulations that includes cross-linked HA have been created to improve the effectiveness as well as durability of IA-HA injections.[64]

HA has many functions in the control of OA knee. It is a good therapeutic choice since it may maintain cartilage health, and also restore the viscoelastic qualities of synovial fluid, as well as have anti-inflammatory action in the knee joint. The selection of HA formulation as well as molecular weight may greatly affect clinical results, thereby stressing the need of customized treatment plans in OA therapy.

Preparation and Administration Protocol

Free-radical scavengers like sorbitol or else mannitol may be used into IA-HA formulations to improve molecular stability as well as extend therapeutic duration in OA knee. With most of the preparations needing storage between 2 to 8°C prior to their use in Knee joint, refrigeration at this temperature needs along with shelf-life restrictions must be closely watched to ensure product integrity in HA compounds. According to Webner et al. (2021), the usual administration technique is aseptic knee preparation with povidone-iodine or chlorhexidine followed by careful joint aspiration to eliminate effusion should exist. The writers underline that injection strategy depends on exact anatomical localization as well as usually uses a lateral or medial patellofemoral approach with the knee in flexion. Injection volumes range from 2-6 mL depending on the specific commercial preparation, with dosing regimens varying from single injections (particularly with cross-linked formulations) to multiple weekly injections (typically 3-5) for non-cross-linked preparations. Commercially available HA formulations vary primarily in their molecular weight (MW), ranging from low-MW to intermediate-MW and high-MW preparations. This molecular weight differentiation significantly influences the rheological properties and synovial retention time of the injectable formulations.[65]

Patient-Specific Factors Affecting Treatment Outcomes

The effectiveness of treatments for OA of the knee, such as PRP and HA, is influenced by a range of patient-specific factors.

1. Age Considerations

Age is a significant determinant of treatment outcomes in OA. As individuals gets older, the regenerative capacity of cartilage diminishes, potentially impacting the efficacy of treatments aimed at promoting cartilage repair, such as PRP.[66] Older patients may also have more advanced joint degeneration, which can limit the effectiveness of interventions like HA that primarily target joint lubrication and inflammation. Moreover, age-related changes in metabolism and immune function can influence the body's response to treatment.[67]

2. **BMI and Obesity Impact**

BMI and obesity are critical factors affecting OA treatment outcomes. The mechanical load on the knee joint is amplified by excess body weight, leading to inflammation and cartilage deterioration. Luo et al.'s meta-analysis highlights that obesity can attenuate the benefits of both PRP and HA treatments, as the added joint load hinders the restoration of normal joint function.[22] Weight management through diet and exercise is often recommended alongside medical treatments to enhance outcomes in overweight and obese patients.

3. **Radiographic Severity**

The severity of OA, as assessed by the Kellgren-Lawrence grading system, is a predictor of treatment success. Patients with lower grades of radiographic severity tend to respond better to interventions like PRP and HA, as these treatments are more effective in early-stage disease where some cartilage integrity is preserved.[6868] In contrast, advanced OA characterized by significant joint space narrowing and osteophyte formation may require more invasive procedures, such as joint replacement.[69]

4. **Previous Treatments and Duration of Symptoms**

The history of previous treatments and the duration of OA symptoms are important considerations in tailoring treatment plans. Patients with a long history of OA symptoms may exhibit less favourable responses to conservative treatments due to chronic joint damage and adaptive changes in pain perception.[70] Additionally, the use of certain medications like steroids, it can affect the efficacy of IA-PRP as well as IA-HA by altering the inflammatory milieu of the knee joint.[71]

5. Comorbidities Affecting Outcomes

Comorbidities such as DM, CVD, as well as metabolic syndrome, can impact OA Knee treatment outcomes. These comorbidities may exacerbate systemic inflammation as well as they may affect the body's ability to repair joint tissues[72] Managing these comorbidities is essential for optimizing treatment efficacy as well as improving overall joint health. Moreover, the presence of psychological comorbidities, such as depression as well as anxiety, can influence pain perception along with treatment adherence, further affecting outcomes.

Combined Therapeutic Approaches

PRP with HA Combination Therapy

The combination of IA-PRP with IA-HA has been extensively studied for its efficacy in the managment of knee OA in many settings. PRP is rich in growth factors that stimulate regeneration of tissue as well as reduce inflammation when injected, while HA restores the viscoelasticity of synovial fluid thereby it was enhancing joint lubrication. A systematic review of several studies done by Zhao et al. (2020) demonstrated that the combination of IA-PRP as well as IA-HA provided best pain alleviation as well as improvement of function on comparison to IA-PRP alone in patients with knee pain.[20] In a similar vein, Yu et al. (2018) found that compared to monotherapy, patients whose treatments included both IA-PRP as well as IA-HA had much better joint function and less discomfort.[73]

Despite the promising results, not all studies agree on the superiority of combination therapy. Baria and their colleagues in their study observed that while IA-PRP as well as IA-HA together provided benefits in reducing pain and improving the outcomes, the addition of IA-HA to IA-PRP did not always result in significant improvements over PRP alone in those patients. These discrepancies highlight the need for further research with higher samples and also to identify patient populations that may benefit most from combination therapies of these two drugs.[74]

Synergistic Effects and Rationale

Combining drugs that target many aspects of the pathophysiology of the illness helps one to treat OA properly. Hallmarks of OA include inflammation, lower joint lubrication, and cartilage degradation. Combining drugs helps one to obtain complete treatment of OA symptoms by addressing many routes simultaneously. Combining the lubricating and viscoelastic properties of HA with the regenerative and anti-inflammatory effects of PRP, for example, IA-PRP and IA-HA, is thought to offer synergistic benefits. More successful than any one treatment, this combo could help joints function better and ease pain.[75]

Clinical Evidence for Combination Approaches

Different combination treatments for knee OA have been investigated clinically as well as shown possible advantages. Combining therapy in OA knee should lower pro-inflammatory mediators and support cartilage healing, thus improving patient outcomes, according a 2020 Grässel and Muschter research.[76] Filardo et al. (2016) also underlined the therapeutic practice of combining non-surgical therapies with pharmaceutical interventions to get better pain control and also enhanced functioning in early OA patients.[77]

Combining therapy modalities is a good way to improve clinical results for knee OA. Treatments like IA-PRP as well as IA-HA used in concert may target many disease processes, therefore offering complete symptom control. However, variability in clinical responses underscores the importance of personalized treatment plans tailored to individual patient needs.

Relevant articles

1. Chandran et al. (India, 2022) compared intra-articular PRP with corticosteroid injections in 60 knee OA patients. Participants received three injections at 2-week intervals (PRP group) or single methylprednisolone injection (corticosteroid group). The WOMAC and VAS ratings were used to evaluate the outcomes at the 1, 3, and 6-month marks. While corticosteroids shown stronger short-term benefits at 1 month, PRP outperformed them at 3 and 6 months in terms of pain reduction and functional improvement. The study concluded PRP offers more sustained therapeutic benefits.[7]
2. Jalali Jivan et al. (Iran, 2021) conducted an open-label trial comparing intra-articular PRP versus HA in 102 knee OA patients. Participants received three weekly injections of either IA-PRP or IA-HA. Funcational status were analysed using WOMAC, VAS, as well as Lequesne scores at 3 and 6 months. Both treatments showed significant improvement, but PRP demonstrated superior results in pain reduction and functional improvement at both follow-up periods. The study concluded IA-PRP was more effective than IA-HA for knee OA management.[8]

3. In 50 patients with knee OA, Dinesh et al., (India, 2020) compared IA-PRP to IA-HA injections. Participants had three weekly injections of either IA-PRP or IA-HA. While both treatments improved, at all follow-up times PRP showed notably greater pain alleviation and functional results. For mild to severe knee OA in this study, the research found that PRP outperformed HA in those patients.[5]
4. In 75 knee OA patients, Sathyamurthy et al., (India, 2022) compared intra-articular autologous PRP with HA in this study. HA group had one weekly injection; PRP group got three. VAS and WOMAC ratings used to evaluate outcomes in those patients. Although both treatments worked well, PRP was found to be the better option in terms of pain relief and functional outcomes throughout all follow-up times. When comparing PRP with HA for the treatment of knee OA, the research found that PRP had better long-term effects.[6]
5. Huang et al. (Taiwan, 2022) conducted a RCT comparing single injections of PRP combined with different hyaluronans in 120 knee OA patients. Participants received PRP + HYAJOINT Plus, PRP + Hyalgan, or PRP alone. Outcomes were assessed using WOMAC, VAS, along with Lequesne scores. Results showed all treatments improved outcomes, but PRP + HYAJOINT Plus demonstrated superior and more sustained effects. The study concluded combined therapy with specific HA formulations enhances therapeutic efficacy.[78]

6. Sun et al. (Taiwan, 2021) compared single crosslinked hyaluronan (HYAJOINT Plus) with PRP versus PRP alone in 150 knee OA patients. Participants received single injections of either combined therapy or PRP alone. Outcomes were assessed using WOMAC, VAS, plus EuroQol-5D scores. There was a statistically significant improvement in reduction of pain plus performance results over the subsequent follow-up period for patients who received combined treatment. The study concluded HYAJOINT Plus with PRP provides superior therapeutic benefits compared to PRP alone.[79]
7. Dório et al. (Brazil, 2021) conducted a RCTl evaluating PRP and plasma efficacy in 62 knee OA patients. Participants gotten 3 weekly injections of either PRP, plasma, or saline. Outcomes were assessed using WOMAC, VAS, and SF-36 scores. When compared to the placebo group, both the PRP and plasma groups exhibited considerable improvements in pain and function; however, the PRP group showed even better benefits. The study concluded both PRP and plasma are effective treatments for knee OA.[80]
8. Fifty individuals identified as having early-stage knee osteoarthritis were studied by Saravanan et al. (India, 2022). Each participant got an injection of HA once. At3,6, and 12 months, outcomes were evaluated using VAS and WOMAC ratings. Significant reductions in pain and functional impairment were seen across all time points of follow-up. Results showed that HA is an effective therapy for early-stage knee OA, with the greatest

improvement shown between three and six months after treatment began, and thereafter a progressive decrease in effectiveness.[9]

9. Luo et al. (China, 2020) conducted a meta-analysis comparing PRP and HA for knee OA in overweight/obese patients. The analysis included 11 studies with 1,129 patients. Outcomes were assessed using WOMAC and VAS scores. In individuals who were overweight or obese, the results demonstrated that PRP offered better enhancement in function as well as pain alleviation than HA. The study concluded PRP should be preferred over HA for knee OA treatment in this population.[22]
10. Raeissadat et al. (Iran, 2015) conducted a one-year RCT comparing IA-PRP and IA-HA in 160 knee OA patients. Participants received two PRP injections or three weekly HA injections. Outcomes were assessed using WOMAC, SF-36, and VAS scores at 2, 6, and 12 months. At 12 months, PRP showed much greater functional results and pain alleviation compared to the other therapy, while both were effective. Results showed that PRP outperformed HA in the long run.[12]
11. Di Martino et al. (Italy, 2019) conducted a RCT comparing PRP and HA in 192 knee OA patients. Participants received three weekly injections of either IA-PRP or IA-HA, with retreatment at 1 year. Outcomes were assessed using IKDC, KOOS, VAS, and Tegner scores. PRP showed better results at 2 years, but differences were not significant at 5 years. Both

groups showed significant improvement from baseline. The study concluded both treatments are effective with similar long-term outcomes.[19]

12. Kesiktas et al. (Turkey, 2020) conducted a randomized study comparing IA-HA, and IA-PRP injections in 90 knee OA patients. Outcomes were assessed via WOMAC, VAS, and quality of life questionnaires. Results demonstrated all interventions improved pain and function, with the peptide group showing superior outcomes at month 1 but equivalent results at month 3. The authors concluded that single-dose peptide injections offer a viable, cost-effective alternative with rapid-onset efficacy comparable to HA and PRP in short-term management.[81]
13. Zhao et al. (China, 2020) examined the efficacy and safety of combined PRP plus HA versus monotherapy in knee OA. The analysis included 9 studies with 1,315 patients. Outcomes were assessed using WOMAC and VAS scores. Results demonstrated that combination therapy yielded significantly better pain relief and functional improvement than HA alone at 6 and 12 months, with mixed results versus PRP monotherapy. The authors concluded that PRP+HA offers superior long-term efficacy with excellent safety compared to HA alone. [20]
14. Zhang et al. (China, 2022) conducted a systematic review and meta-analysis evaluating PRP+HA combination versus PRP alone for knee OA. Analysis included 8 studies with 761 patients. Outcomes were assessed via VAS along with WOMAC scores. Results demonstrated that combination

therapy provided superior pain relief and functional improvement at most timepoints, particularly long-term follow-up. The authors concluded that PRP+HA combination offers enhanced therapeutic efficacy over PRP monotherapy, with similar safety profiles and potentially complementary biological mechanisms.[21]

15. Cole et al. (USA, 2017) conducted a prospective, double-blind randomized controlled trial comparing HA versus PRP in 111 patients with knee OA. Participants received three weekly injections of either intervention. Outcomes were assessed using WOMAC, IKDC, and VAS scores. Results demonstrated that PRP provided significantly greater improvement in WOMAC pain scores and IKDC scores at 24 and 52 weeks. The authors concluded that PRP offers superior clinical efficacy with better biological effects than HA for knee OA treatment.[82]

16. Moretti et al. (Italy, 2022) conducted a prospective clinical study evaluating PRP injections in 60 patients with grade I-II knee OA. Participants received three PRP injections at 15-day intervals. Outcomes were assessed using KOOS, IKDC, and VAS scores at 15 days, 3, 6, and 12 months. Results demonstrated significant improvement across all parameters throughout the follow-up period, with peak improvement at 3 months. The study's authors found that individuals with early-stage knee OA who had PRP injections saw significant improvements in both pain and function in the middle of the treatment period. [83]

17. Belk et al. (USA, 2021) performed a systematic review and meta-analysis comparing PRP versus HA for knee OA. Analysis included 18 randomized controlled trials with 811 patients receiving PRP and 797 receiving HA. Outcomes were assessed via WOMAC, IKDC, VAS, and EQ-VAS scores. The results showed that at every timepoint (1-12 months), PRP outperformed HA in terms of pain alleviation and enhancement in function. They observed that PRP has a superior therapeutic option on comparison to HA for knee OA management. [17]
18. Using constant injection ratios, Wu and their colleagues performed a meta-analysis contrasting IA-PRP to IA-HA in knee OA. 10 RCTs totaling 1,069 patients were included in their analysis. WOMAC, VAS, IKDC, as well as Lequesne ratings were used to evaluate outcomes in those patients to assess functional status. Particularly in younger people suffering from moderate to severe OA, the findings of this study revealed that PRP was much more efficient than HA in lowering pain and enhancing function in those patients. The authors finally concluded that IA-PRP offered superior long-term therapeutic efficacy on comparison to IA-HA.[84]
19. Tang and their colleagues did a meta-analysis comparing IA-PRP versus IA-HA in knee OA treatment. Those analysis included RCTs with 1,350 patients. Functional status were assessed via VAS and WOMAC scores. When compared to HA, the results showed that PRP considerably improved functional capacity and pain alleviation in those patients. The

authors concluded that PRP constitutes a more effective therapeutic intervention than HA for knee OA management, with greater long-term efficacy and comparable safety profile.[18]

20. Raeissadat et al. (Iran, 2021) conducted a one-year randomized clinical trial comparing PRP, PRGF, HA, and ozone injections in 238 knee OA patients. Outcomes were assessed using WOMAC as well as VAS scores at 2, 6, and 12 months. Results demonstrated that all treatments provided significant improvement, with PRP showing superior results at 6 and 12 months. The authors concluded that PRP offers greater long-term therapeutic efficacy than other intra-articular injections.[85]
21. Dallari et al. (Italy, 2016) conducted a RCTs comparing ultrasound-guided injections of PRP, HA, and PRP+HA in 111 patients with hip OA. Participants received three weekly injections. Outcomes were assessed using VAS, WOMAC, and HHSs at 2, 6, and 12 months. The results showed that compared to HA alone, PRP or PRP with HA considerably improved pain alleviation and operational results. The authors concluded that PRP represents a superior therapeutic option for hip OA, with PRP+HA combination showing comparable efficacy to PRP monotherapy.[86]

Injection Protocols and Technical Considerations in OA Knee Treatment

Single versus Multiple Injections

Efficiency as well as patient compliance drive the argument between single vs several injections for patients with knee OA. Although single injections may help, evidence points to numerous injections maybe offering improved joint functioning as well as extended pain alleviation. Early-stage OA was investigated methodically by Vilchez-Cavazos et al. (2019) and these authors found that many rather than one IA-PRP injection enhanced joint function.[87] In patients with early OA, Görmeli et al. (2017) also found that three IA-PRP injections produced better results than IA-HA or single injections. [88]

Optimal Dosing and Intervals

Maximizing therapeutic results depends on knowing the best dosage as well as timing for injections. While studies indicate that three injections at one-week intervals may provide the greatest results for PRP, the proper dose of HA differs. Depending on the formulation as well as patient's reaction, IA-HA injections—which are commonly given weekly over a three to five-week period—are sometimes given Han et al. (2019) underlined the need of customizing the dose schedule to the particular condition and reaction to treatment of the patient.[89]

Preparation Techniques and Standardization

Unstandardized preparation of PRP as well as HA injections results in variation in clinical outcomes of patients with OA knee. This variety results from many centrifugation techniques, platelet activation strategies, and also some of the HA compositions.[90]Efforts made at standardizing concentrate on besting preparation methods to guarantee uniformity as well as effectiveness. Emphasizing the requirement of uniform methods to raise the dependability of injectable treatments in knee OA, Billesberger et al. (2020) [91]

USG versus Landmark-Based Injections

In knee OA therapy, a major technical factor is the decision between landmark-based and ultrasonic-guided injections. Higher accuracy and precision provided by ultrasonic guiding help to lower the danger of erroneous needle insertion by means of improved patient outcomes. Better treatment outcomes resulted from ultrasounds-guided injections shown by Wu et al. (2016) as they were more accurate than landmark-based techniques.[92] Ruiz et al. (2019) underlined again how better ultrasonic guiding is in reducing procedure problems and improving patient comfort.[93]

Research Gaps and Future Directions

Standardization Needs in PRP Preparation

Variations in centrifugation speed, platelet concentration, and activation techniques provide variable findings, therefore confounding comparisons across research.[94] To guarantee consistency in clinical results and to help to create clear treatment recommendations, standardization of PRP preparation is very vital. [95]

Ideal criteria for patient selection

Maximizing the effectiveness of PRP and HA treatments depends on selecting appropriate patients. According to present studies, the degree of OA, age, BMI, and other elements might affect the efficacy of therapy.[96] By means of exact patient selection criteria grounded on these factors, therapy results may be improved and the chance of poor responses can be reduced.[97]

Data Requirements for Long-Term Outcomes

Although short-term results of HA and PRP are well-documented, long-term effects are not very clear-cut. To evaluate the lifetime of therapeutic effects and to grasp any hazards related to recurrent injections, longitudinal studies are required. Such information is very essential for guiding doctors and patients on the long-term effectiveness of these therapies.[20]

Requirement for Biomarker Research to Foretell Responders

Biomarkers might help to forecast which patients will benefit from PRP and HA treatments. Finding biomarkers that match clinical response might help to create individualized treatment regimens, thereby maximizing results and allocation of resources.[98] Verifying these biomarkers and incorporating them into clinical practice should be the main priorities of further studies.[99]

Novel Combined Therapeutic Approaches

Exploring novel combined therapeutic approaches could enhance the efficacy of OA treatments. Combining PRP and HA with other modalities, such as physical therapy or pharmacological agents, may offer synergistic benefits.[100] Research into these combinations should aim to identify optimal protocols and patient populations that would benefit most from such integrative strategies.[101]

Addressing these research gaps is essential for advancing the treatment of knee OA with PRP and HA. By focusing on standardization, patient selection, long-term outcomes, biomarker integration, and combined therapies, future research can pave the way for more effective and personalized treatment strategies.

MATERIALS AND METHODS

Study Design and Study Setting

A prospective, randomized controlled comparative study was conducted at R.L. Jalappa Hospital and Research Center, affiliated with Sri Devaraj Urs Medical College under SDUAHER. This tertiary care teaching hospital provided an appropriate clinical setting for investigating therapeutic interventions for knee OA.

Study Period

The study was conducted over an 18-month period from May 2023 to October 2024.

Inclusion Criteria

(1) age between 40-80 years

(2) clinical and radiographic diagnosis of primary knee OA

(3) Kellgren-Lawrence radiographic severity grades I-III

(4) inadequate response to prior conservative management including analgesics, physical therapy, or activity modification

(5) bilateral knee OA.

Exclusion Criteria

(1) platelet count below 150,000/cu.mm

(2) haemoglobin level below 10 g/dl

(3) uncontrolled diabetes mellitus (HbA1c >8.5%)

(4) history of previous trauma or surgical intervention to the affected knee

(5) active cutaneous lesions or infections at the intended injection site

(6) concurrent antiplatelet or anticoagulant therapy.

Sample Size Estimation

The sample size was calculated based on the findings reported by Dinesh et al. (2020), who compared PRP and HA injections in 30 patients with knee OA in India.[5] Their study reported mean differences in WOMAC scores between pre-intervention and 6-week post-intervention assessments of 2.433 ± 0.228 and 2.167 ± 0.47 for the PRP and HA groups, respectively.

Using these values at 95% confidence interval (CI) and 80% power, a sample size of 22 patients per group was determined using the formula:

$N = 2\ SD^2 (Z\alpha/2 + Z\beta)^2 / d^2$

Where $Z\alpha/2$ represents the critical value of the Normal distribution at $\alpha/2$ (1.96 for 95% CI), Zβ denotes 0.84 for 80% power),

SD represents the standard deviation from the reference population, and

d represents the largest difference between two means.

The sample size calculation was validated using MedCalc statistical software to ensure adequate statistical power for detecting clinically significant differences between interventions.

Sampling Method

Consecutive patients with symptoms of knee OA arriving to the orthopaedic outpatient department were assessed for eligibility using the specified inclusion and exclusion criteria. Appropriate patients who granted informed permission were registered in the trial and randomized into two equal intervention groups using a computer-generated random number sequence. The second group had HA injected into the joint; the first group received PRP injected there. Randomizing helps to ensure that the intervention groups had same baseline characteristics and served to reduce the possibility of selection bias. This improved the consistency of the comparison analysis.

Intervention

All patients were evaluated clinically before any intervention began, including thorough patient history collection, physical examination, and radiographic evaluations. The PRP group's patients had 30 ml of venous blood drawn into acid-citrate-dextrose tubes, and then they followed a conventional double-centrifugation procedure to get 4–5 ml of PRP that was low in white blood cells. Calcium chloride was added to the PRP just before injection to activate it.

For patients assigned to the HA group, a standardized preparation of high molecular weight (1500-2000 kDa) HA was utilized. All injections were administered under strict aseptic conditions using a lateral parapatellar approach with the knee in 90° flexion. Post-injection, all patients were advised to rest for 24-48 hours and avoid strenuous activities for one week. Standard post-procedural analgesics were permitted, if necessary, with documentation of any additional medication use.

Data Collection Procedure

Demographic data including age, gender, BMI, comorbidities, and duration of symptoms were recorded at baseline using a standardized proforma. Clinical and functional assessments were conducted at baseline (pre-intervention) and at 2 weeks, 6 weeks, and 3 months post-intervention by trained orthopaedic specialists blinded to the intervention group allocation.

We used the VAS, a 10-point scale with 0 representing no pain and 10 representing the most excruciating agony conceivable, to evaluate the level of discomfort. The VAS has demonstrated high reliability (ICC>0.80) and validity in previous studies evaluating knee OA interventions.[82]

A functional evaluation was carried out with the WOMAC, a validated disease-specific instrument with 24 items split into three subscales: physical function (17 items), pain (5 items), and stiffness (2 items). A total of 96 potential scores are generated using the 5-point Likert scale, where 0 represents no opinion and 4 represents strong disagreement. In terms of pain, stiffness, and functional restrictions, higher ratings suggest worsening symptoms. It has demonstrated excellent internal consistency, test-retest reliability, and construct validity in multiple studies assessing therapeutic interventions for knee OA.[12]

Utilizing the KL classification system, a well recognized grading system that runs from 0 (absence of radiographic signs of OA) to 4 (severe OA characterized by substantial narrowing of the joint space, subchondral sclerosis, and osteophyte production), radiographs were taken to determine the severity of OA.

The safety profile of both therapies was evaluated by meticulously documenting all adverse events and consequences during the research period.

Data Analysis

Statistics were analyzed with SPSS version 25.0. Data on demographics and initial clinical traits were given using descriptive statistics. Continuous variables were shown as means with standard deviations or medians with interquartile ranges, depending on the situation. Categorical variables were shown as rates and percentages.

For intragroup analysis of temporal changes in VAS and WOMAC scores, paired t-tests were employed to compare baseline values with each subsequent assessment timepoint, as well as between consecutive assessment timepoints. For intergroup comparative analysis, independent t-tests were utilized to compare mean VAS and WOMAC scores between PRP and HA groups at each assessment timepoint, as well as the mean differences in these scores from baseline to each follow-up point.

RESULTS

Table 3: Age Distribution

Age in years		**HA group**	**PRP group**
Mean		54.23	52.41
Median		54.00	53.00
Std. Deviation		3.531	4.677
Minimum		45	42
Maximum		60	60
Percentiles	25	53.00	49.50
	50	54.00	53.00
	75	56.25	55.25

The HA group demonstrated a mean age of 54.23 years (median 54.00, SD 3.531) with a range of 45-60 years. The PRP group showed a slightly younger profile with a mean age of 52.41 years (median 53.00, SD 4.677) with a range of 42-60 years.

Table 4: Gender Distribution

Gender	HA group		PRP group	
	n	%	n	%
Female	16	72.7	13	59.1
Male	6	27.3	9	40.9
Total	22	100.0	22	100.0

In the HA group (n=22), there is a notable female predominance with 16 females (72.7%) compared to 6 males (27.3%). The PRP group (n=22) demonstrates a more balanced gender distribution with 13 females (59.1%) and 9 males (40.9%).

Figure 10: **Gender Distribution**

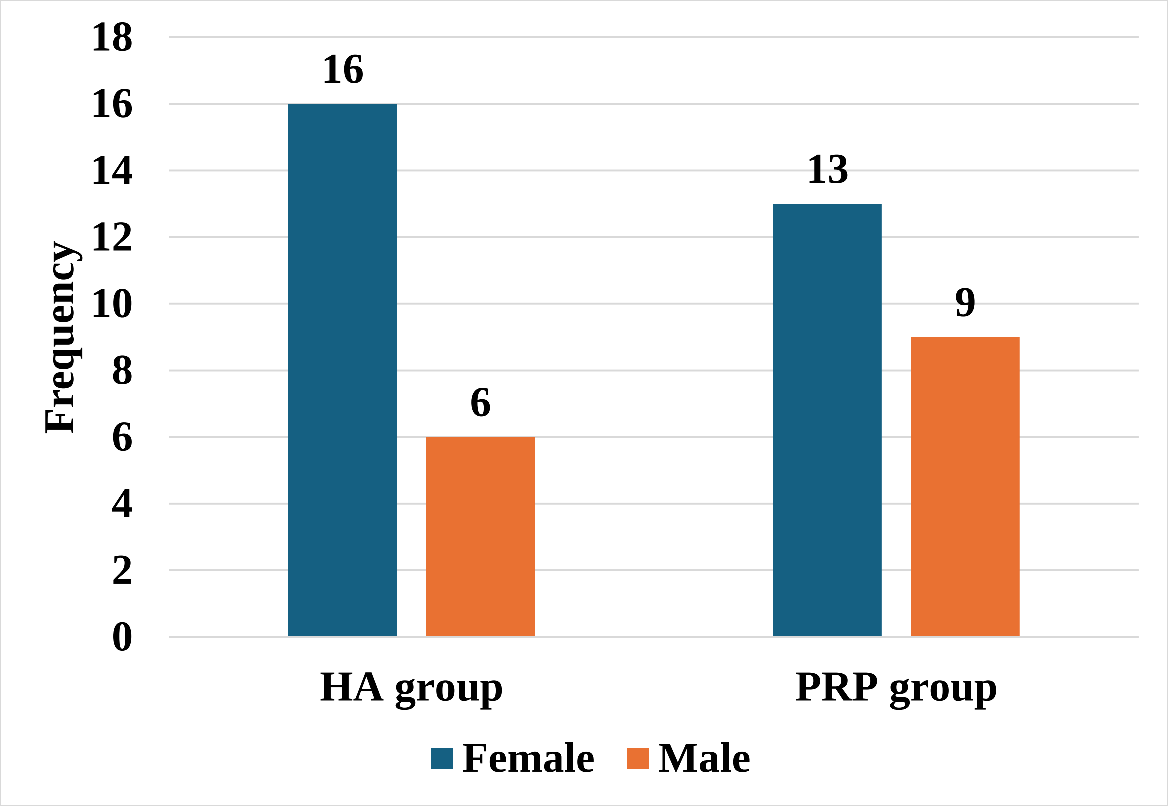

Table 5: Distribution of Comorbidities

Co-morbidities	HA group		PRP group	
	n	%	n	%
DM	17	77.3	15	68.2
HTN and DM	1	4.5	4	18.2
Nil	4	18.2	3	13.6
Total	22	100.0	22	100.0

Diabetes mellitus (DM) represents the most prevalent comorbidity in both cohorts, affecting 17 patients (77.3%) in the HA group and 15 patients (68.2%) in the PRP group. Hypertension with diabetes was observed in 1 patient (4.5%) in the HA group versus 4 patients (18.2%) in the PRP group. Notably, 4 patients (18.2%) in the HA group and 3 patients (13.6%) in the PRP group had no identified comorbidities.

Figure 11: Distribution of Comorbidities

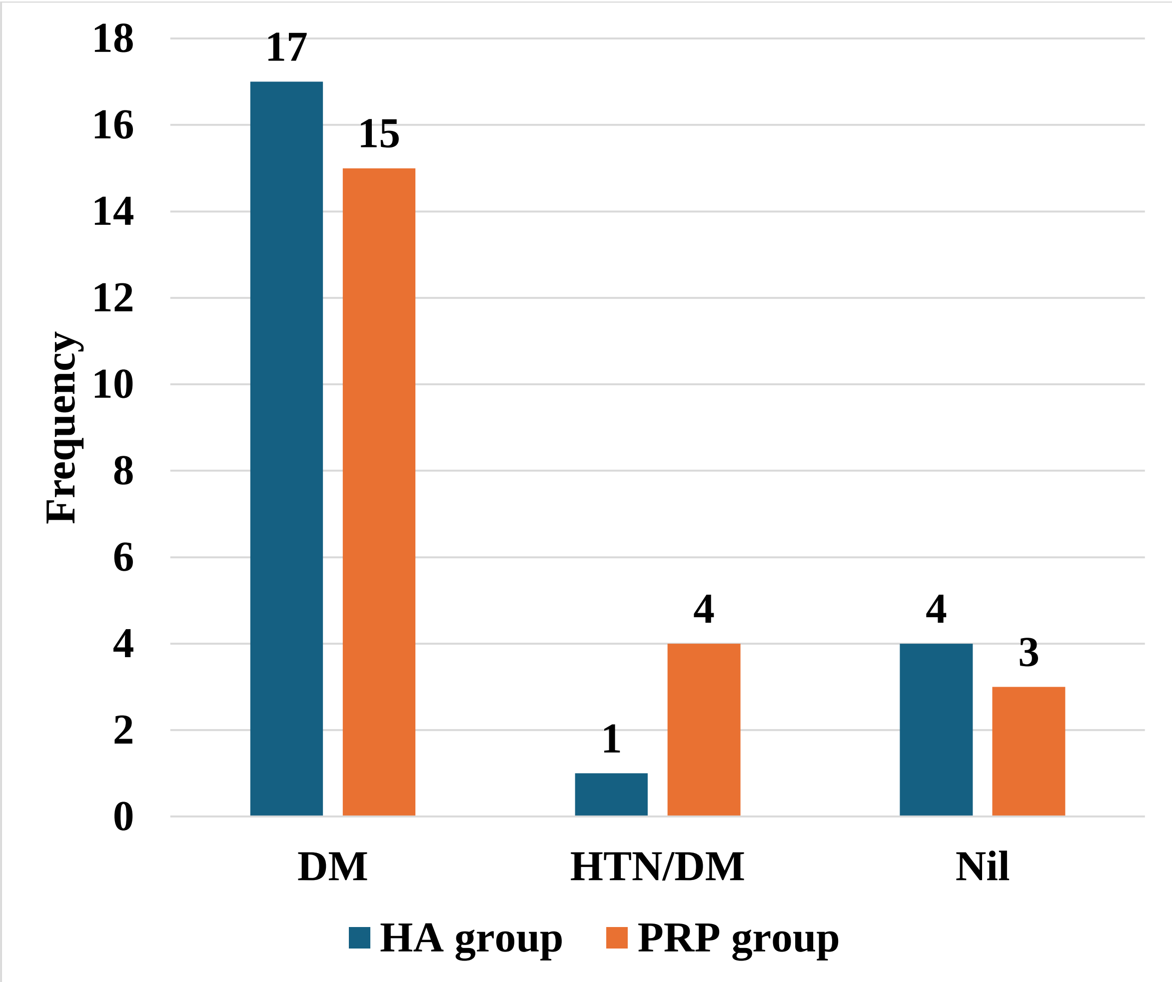

Table 6: Radiographic Grading of OA According to KL Classification

Grading of OA	HA group		PRP group	
	n	**%**	**n**	**%**
II	19	86.4	19	86.4
III	3	13.6	3	13.6
Total	22	100.0	22	100.0

Distribution patterns were remarkably similar between groups, with grade II OA predominating in both the HA group (19 patients, 86.4%) and the PRP group (19 patients, 86.4%). Grade III OA was equally represented with 3 patients (13.6%) in each treatment group.

Figure 12: **Radiographic Grading of OA According to KL Classification**

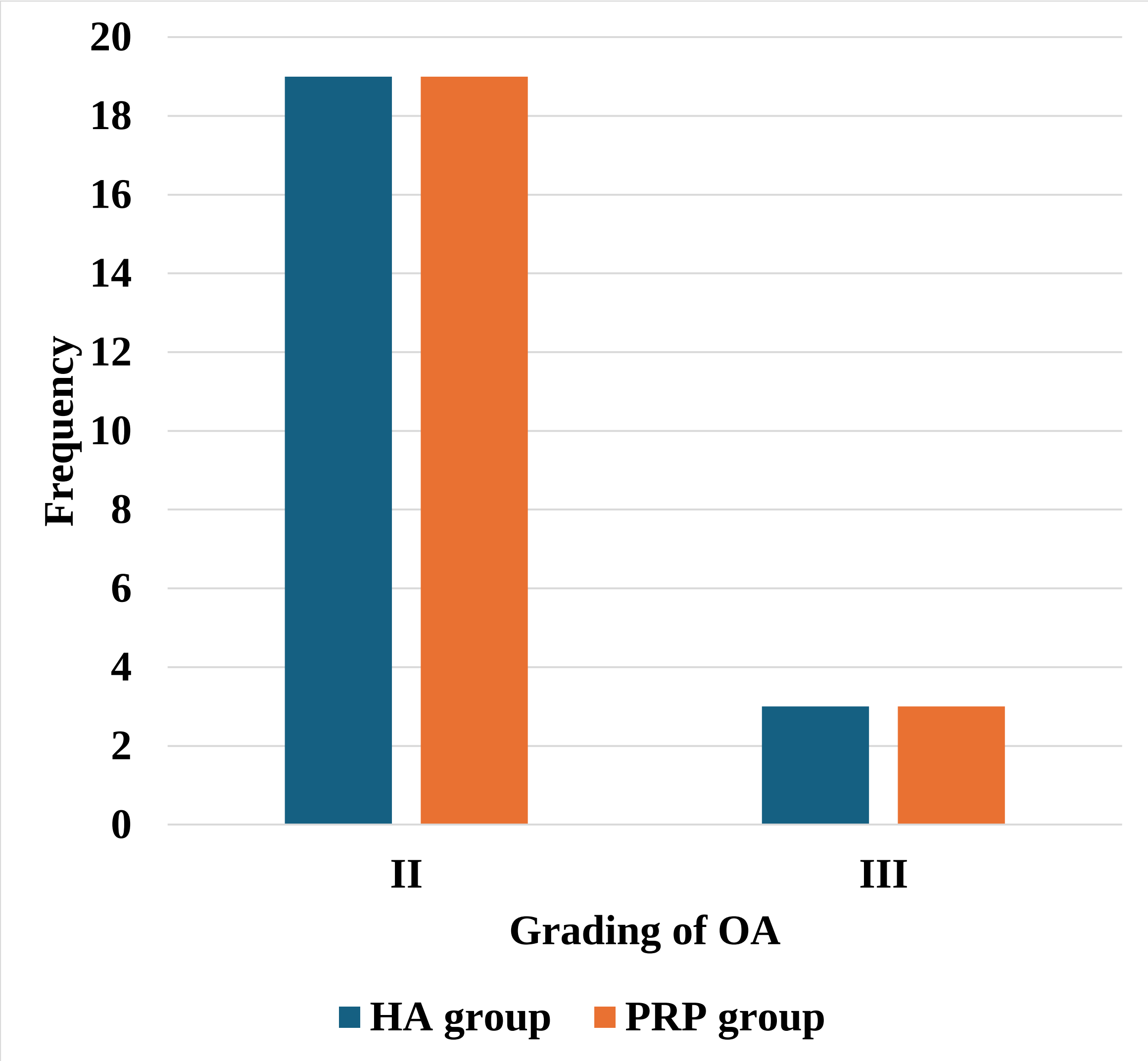

Table 7: Duration of Knee Pain

Duration of Knee pain in months		**HA group**	**PRP group**
Mean		7.18	6.82
Median		7.00	7.00
Std. Deviation		1.943	2.152
Minimum		3	4
Maximum		12	14
Percentiles	25	6.00	5.00
	50	7.00	7.00
	75	8.25	8.00

The HA cohort reported knee pain for a mean duration of 7.18 months (median 7.00, SD 1.943) with a range of 5-12 months. The PRP group demonstrated a similar profile with a mean duration of 6.82 months (median 7.00, SD 2.152) with a range of 4-14 months.

Table 8: **Temporal Progression of Mean VAS Pain Scores**

Group	Measures of VAS scale	Baseline	2 weeks	6 weeks	3 months
HA	Mean	5.05	3.73	3.32	2.77
	Std. Deviation	.213	.456	.568	.612
PRP	Mean	5.14	3.32	2.23	1.14
	Std. Deviation	.351	.477	.429	.351

The HA group demonstrated baseline VAS of 5.05 (SD 0.213), which decreased to 3.73 (SD 0.456) at 2 weeks, 3.32 (SD 0.568) at 6 weeks, and 2.77 (SD 0.612) at 3 months. The PRP group showed baseline VAS of 5.14 (SD 0.351), decreasing to 3.32 (SD 0.477) at 2 weeks, 2.23 (SD 0.429) at 6 weeks, and 1.14 (SD 0.351) at 3 months.

Figure 13: **Temporal Progression of Mean VAS Pain Scores**

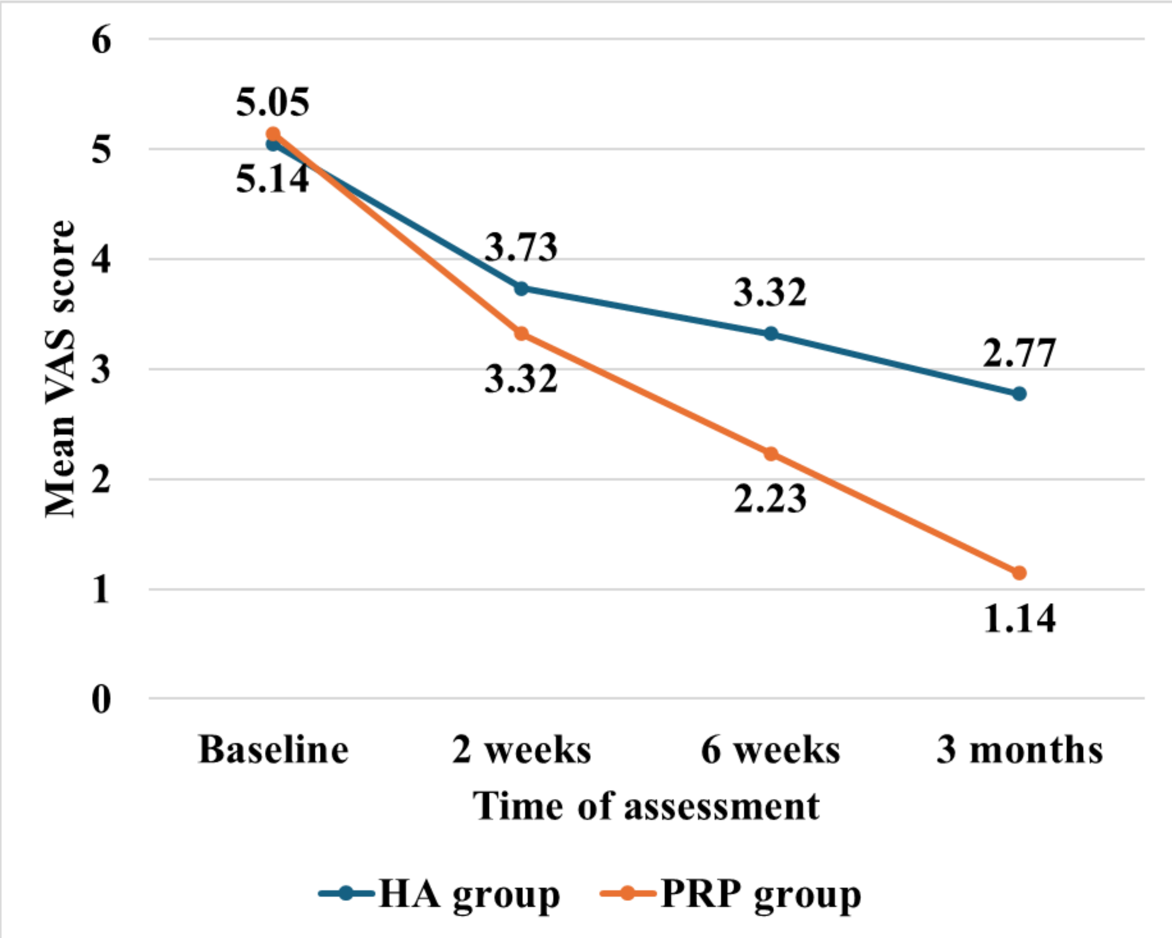

Table 9: Temporal Progression of Mean WOMAC Scores

Group	Measures of WOMAC score	Baseline	2 weeks	6 weeks	3 months
HA	Mean	69.45	66.91	64.64	62.64
	Std. Deviation	11.484	11.710	11.557	11.462
PRP	Mean	74.68	67.14	59.50	53.50
	Std. Deviation	6.743	6.042	6.816	6.530

The HA group demonstrated baseline WOMAC of 69.45 (SD 11.484), which improved to 66.91 (SD 11.710) at 2 weeks, 64.64 (SD 11.557) at 6 weeks, and 62.64 (SD 11.462) at 3 months. The PRP group showed baseline WOMAC of 74.68 (SD 6.743), improving to 67.14 (SD 6.042) at 2 weeks, 59.50 (SD 5.816) at 6 weeks, and 53.50 (SD 6.530) at 3 months. These data reveal that while both interventions improved functional outcomes, the PRP group demonstrated more substantial absolute and relative improvements in WOMAC scores, particularly at later assessment timepoints, suggesting superior long-term functional benefits with PRP treatment.

Figure 14: **Temporal Progression of Mean WOMAC Scores**

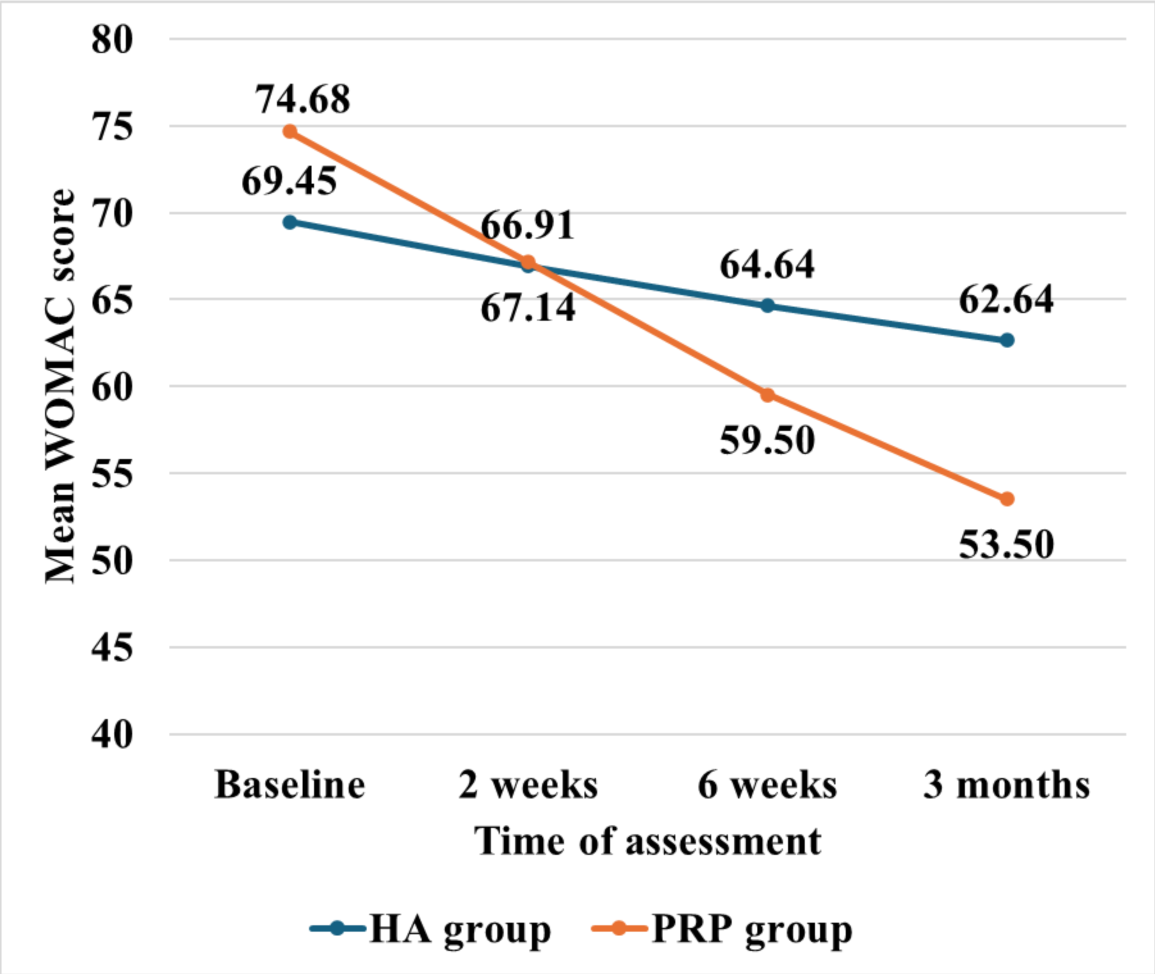

Table 10: Paired T-Test Analysis of VAS Score Changes Over Time in HA Group

Comparison	Mean diff	t-value	p-value
Baseline - 2 weeks	1.32	12.97	0.000
Baseline - 6 weeks	1.73	14.72	0.000
Baseline - 3 months	2.27	16.89	0.000
2 weeks - 6 weeks	0.41	3.81	0.001
2 weeks - 3 months	0.95	7.78	0.000
6 weeks - 3 months	0.55	5.02	0.000

All temporal comparisons demonstrated statistically significant improvements ($p<0.001$ for most comparisons). The mean VAS reduction from baseline to 2 weeks was 1.32 points ($t=12.97$), from baseline to 6 weeks was 1.73 points ($t=14.72$), and from baseline to 3 months was 2.27 points ($t=16.89$). Incremental improvements between consecutive assessment points were also statistically significant, with a 0.41-point reduction from 2 to 6 weeks ($t=3.81$, $p=0.001$) and a 0.55-point reduction from 6 weeks to 3 months ($t=5.02$, $p<0.001$). These data confirm progressive, sustained, and statistically significant pain reduction with HA intervention.

Table 11: Paired T-Test Analysis of VAS Score Changes Over Time in PRP Group

Comparison	Mean diff	t-value	p-value
Baseline - 2 weeks	1.82	17.02	0.000
Baseline - 6 weeks	2.91	25.92	0.000
Baseline - 3 months	4.00	35.10	0.000
2 weeks - 6 weeks	1.09	12.00	0.000
2 weeks - 3 months	2.18	17.39	0.000
6 weeks - 3 months	1.09	12.00	0.000

All temporal comparisons demonstrated highly statistically significant improvements ($p<0.001$ for all comparisons). The mean VAS reduction from baseline to 2 weeks was 1.82 points ($t=17.02$), from baseline to 6 weeks was 2.91 points ($t=25.92$), and from baseline to 3 months was 4.00 points ($t=35.10$). Incremental improvements between consecutive assessment points were also statistically significant, with a 1.09-point reduction from 2 to 6 weeks ($t=12.00$) and a 1.09-point reduction from 6 weeks to 3 months ($t=12.00$). These data demonstrate progressive, substantial, and highly statistically significant pain reduction with PRP intervention, with notably larger effect sizes than observed in the HA group.

Table 12: Paired T-Test Analysis of WOMAC Score Changes Over Time in HA Group

Comparison of mean WOMAC scores in HA group	**Mean difference**	**Paired T test t-value**	**p-value**
Baseline - 2 weeks	2.55	5.72	0.000
Baseline - 6 weeks	4.82	10.29	0.000
Baseline - 3 months	6.82	9.51	0.000
2 weeks - 6 weeks	2.27	9.17	0.000
2 weeks - 3 months	4.27	8.59	0.000
6 weeks - 3 months	2.00	6.48	0.000

All temporal comparisons demonstrated statistically significant improvements ($p<0.001$ for all comparisons). The mean WOMAC reduction from baseline to 2 weeks was 2.55 points ($t=5.72$), from baseline to 6 weeks was 4.82 points ($t=10.29$), and from baseline to 3 months was 6.82 points ($t=9.51$). Incremental improvements between consecutive assessment points were also statistically significant, with a 2.27-point reduction from 2 to 6 weeks (t=9.17) and a 2.00-point reduction from 6 weeks to 3 months (t=6.48). These data confirm progressive, sustained, and statistically significant functional improvement with HA intervention.

Table 13: Paired T-Test Analysis of WOMAC Score Changes Over Time in PRP Group

Comparison	Mean diff	t-value	p-value
Baseline - 2 weeks	7.55	11.66	0.000
Baseline - 6 weeks	15.18	14.72	0.000
Baseline - 3 months	21.18	15.81	0.000
2 weeks - 6 weeks	7.64	13.10	0.000
2 weeks - 3 months	13.64	14.60	0.000
6 weeks - 3 months	6.00	8.90	0.000

All temporal comparisons demonstrated highly statistically significant improvements ($p<0.001$ for all comparisons). The mean WOMAC reduction from baseline to 2 weeks was 7.55 points (t=11.66), from baseline to 6 weeks was

15.18 points (t=14.72), and from baseline to 3 months was 21.18 points (t=15.81). Incremental improvements between consecutive assessment points were also statistically significant, with a 7.64-point reduction from 2 to 6 weeks (t=13.16) and a 6.00-point reduction from 6 weeks to 3 months (t=8.90). These data demonstrate progressive, substantial, and highly statistically significant functional improvement with PRP intervention, with notably larger effect sizes than observed in the HA group.

Table 14: Independent T-Test Comparison of VAS Scores at Different Assessment Timepoints

Time of assessment of VAS score	Intervention group	Mean diff	t-value	p-value
Baseline	HA	-0.091	-1.038	0.305
	PRP			
2 weeks	HA	0.409	2.909	0.006
	PRP			
6 weeks	HA	1.091	7.190	0.000
	PRP			
3 months	HA	1.636	10.878	0.000

	PRP			

This table presents intergroup comparative analysis of VAS pain scores. At baseline, there was no statistically significant difference between groups (mean difference -0.091, t=-1.038, p=0.305), confirming baseline homogeneity. By 2 weeks, the PRP group demonstrated statistically significantly better pain relief (mean difference 0.409, t=2.909, p=0.006). This advantage increased at 6 weeks (mean difference 1.091, t=7.190, p<0.001) and further at 3 months (mean difference 1.636, t=10.878, p<0.001). These data demonstrate progressively diverging outcomes between interventions, with PRP demonstrating statistically and clinically significant superiority in pain reduction, particularly in medium to long-term outcomes.

Table 15: Independent T-Test Comparison of WOMAC Scores at Different Assessment Timepoints

Time of assessment of WOMAC score	Intervention group	Mean diff	t-value	p-value
Baseline	HA	-5.227	-1.841	0.073
	PRP			
2 weeks	HA	-0.227	-0.081	0.936
	PRP			
6 weeks	HA	5.136	1.796	0.08
	PRP			
3 months	HA	9.136	3.248	0.002
	PRP			

This table presents intergroup comparative analysis of WOMAC functional scores. Statistical significance was not achieved, however there was a trend toward higher baseline dysfunction in the PRP group (mean difference -5.227, t=-1.841, p=0.073). There was a little but insignificant difference at the 2-week mark (mean difference -0.227, t=-0.081, p=0.936). The PRP group showed better function after 6 weeks, with a 5.136-point advantage; nevertheless, this was close to but not statistically significant (t=1.796, p=0.08). The PRP group showed 9.136-point superior functional results at 3 months (t=3.248, p=0.002) compared to the control group. These data suggest that PRP provides superior functional improvement compared to HA, with the difference becoming more pronounced and statistically significant at longer-term assessment points.

DISCUSSION

Injecting PRP or HA into the joint of a patient with mild to moderate knee OA significantly improves functional outcomes and decreases discomfort, according to this RCT. However, our findings reveal a clear therapeutic advantage for PRP over HA, particularly in medium to long-term outcomes at 6 weeks and 3 months post-intervention. This comparative efficacy pattern provides important insights for clinical decision-making in the conservative management of knee OA.

Our study's demographic profile is consistent with established epidemiological patterns in knee OA, with female predominance (72.7% in HA group, 59.1% in PRP group) and mean age in the sixth decade (54.23 years in HA versus 52.41 years in PRP). This aligns with multiple previous investigations including Raeissadat et al. (2015), who reported similar demographic characteristics (mean age 56.85 years in PRP group, 61.13 years in HA group; 70% female) in their randomized trial of 160 patients with knee OA in Iran.[12] The high prevalence of diabetes mellitus as a comorbidity in our study population (77.3% in HA group, 68.2% in PRP group) reflects the common pathophysiological pathways between metabolic disorders and OA, as recognized in recent literature.[22]

At all evaluation timepoints compared to the starting point, the intragroup analysis for both therapies showed statistically noteworthy enhancements in VAS and WOMAC ratings ($p<0.001$), confirming that both modalities were effective in their treatment. The average VAS score for the HA group went down from 5.05 at start to 2.77 at end, a 45.1% drop, and the WOMAC score went up from 69.45 to 62.64, a 9.8% improvement. These findings are comparable to those reported by Saravanan et al. (2022), who demonstrated significant symptomatic and functional improvements following HA injection in 50 patients with early knee OA in India, with WOMAC score improvements from 74.28 at baseline to 67.56 at 12 weeks.[9]

The superior efficacy of PRP observed in our study is evidenced by the more substantial improvements in both pain and functional parameters. VAS scores in the PRP group decreased from 5.14 at baseline to 1.14 at 3 months (77.8% reduction), while WOMAC scores improved from 74.68 to 53.50 (28.4% enhancement). The magnitude of this improvement exceeds that reported by Moretti et al. (2022) in their prospective study of 50 patients with knee OA in Italy, where PRP injection resulted in a 57.2% reduction in pain scores at 3 months.[83] This difference may be attributed to variations in PRP preparation protocols, injection techniques, or patient selection criteria.

The temporal pattern of improvement observed in our study is particularly noteworthy. While both interventions demonstrated progressive enhancement in outcome measures, the rate and magnitude of improvement were consistently superior in the PRP group. Dinesh et al. (2020) found that both PRP and HA significantly improved WOMAC scores in a comparative analysis of 30 patients.

However, at all evaluation timepoints (2, 6, and 12 weeks), the PRP group showed better results. This conclusion is consistent with that observation.[5]

The comparative analysis between interventions revealed an increasingly divergent efficacy trajectory. At baseline, outcome measures were statistically comparable between groups (p=0.305 for VAS, p=0.073 for WOMAC). However, by 2 weeks, the PRP group demonstrated statistically superior pain reduction (mean difference 0.409, p=0.006), with this advantage progressively increasing at 6 weeks and 3 months. Cole et al. (2017), who compared HA and PRP in 111 American patients with knee OA in a RCT, found similar results with diverging outcomes over time. [82]Their study similarly demonstrated that while both treatments improved WOMAC scores, the PRP group showed significantly greater improvement at 24 and 52 weeks.

The progressively widening efficacy gap between PRP and HA observed in our study supports the biological mechanism of action attributed to PRP. As elucidated by dos Santos et al. (2021) in their comprehensive review, PRP contains numerous growth factors and bioactive proteins that stimulate cellular proliferation, matrix synthesis, and anti-inflammatory effects through multiple signalling pathways.[1414] This may explain the sustained and progressive improvement in the PRP group, as these biological effects continue beyond the immediate post-injection period. In contrast, HA primarily provides viscoelastic supplementation and limited biological modulation of the intra-articular environment, potentially explaining its more modest therapeutic effect.

The superior long-term efficacy of PRP observed in our study is corroborated by meta-analytical evidence. After comparing PRP with HA for knee OA, Belk et al. (2021) found that PRP had far superior results at 6 and 12 months after injection. The study included 18 RCTs with 811 participants.[17]Similarly, after 6 and 12 months follow-up, Wu et al. (2020) discovered that PRP injections offered far superior pain relief and functional improvement than HA. This was based on an analysis of 10 randomized controlled studies including 1069 patients.[102]

The magnitude of improvement in WOMAC scores observed in our PRP group (28.4% enhancement at 3 months) exceeds the MCID threshold established for OA interventions, suggesting that the observed benefits are not merely statistically significant but clinically meaningful. This is reliable with the findings of Raeissadat et al. (2015), who reported clinically significant improvements in WOMAC scores following PRP injection, with superiority over HA at all assessment timepoints up to 12 months.[12]

Our investigation found similar effectiveness between IA-PRP and IA-HA at early evaluation points; divergence becomes more noticeable at later follow-up in the study samples. This temporal trend is consistent with the results of Jalali Jivan et al. (2021), and they have evaluated PRP and HA in 102 patients with knee OA in Iran and showed identical short-term benefits but better long-term outcomes with PRP at 6 months follow-up). This implies that while both treatments might provide quick acute alleviation, the continuous biological effects of PRP help to produce better long-term results.[8]

The comorbidity profile in the present study, more specifically the significant diabetes mellitus prevalence offered important background for understanding of our results. In overweight or obese patients with knee OA, a group often marked by metabolic comorbidities, Luo et al. (2020) performed a meta-analysis especially looking at the effectiveness of PRP vs HA. Despite great frequency of metabolic comorbidities in our cohort, their study of 5 randomized controlled trials with 340 patients found that PRP showed better effectiveness than HA in this particular demographic.[22]

It is possible that our results may not be applicable to more severe cases of OA since the radiographic severity distribution in our research (86.4% KL grade II in both groups) indicates mild to moderate OA. A study conducted in Iran by Raeissadat and their colleagues examined almost 102 patients with knee OA ranging in radiographic severity grades. The patients were compared using numerous IA-PRP and IA-HA. Although IA-PRP showed better effectiveness overall, their results indicated that the benefit was more noticeable in earlier stages of OA knee.[85] This aligns with our observations and underscores the importance of appropriate patient selection for optimal therapeutic outcomes.

The gender distribution in our study, with female predominance in both groups but more pronounced in the HA cohort (72.7% versus 59.1%), introduces potential bias in interpreting our findings. Gender-specific differences in OA pathophysiology and response to therapeutic interventions have been documented in multiple studies. However, Dório et al. (2021) conducted a RCT with 53 patients in Brazil comparing PRP efficacy across gender subgroups and found no significant gender-specific differences in therapeutic response, suggesting that our findings may remain valid despite the gender imbalance between groups.[80]

The similarity in baseline pain chronicity between our intervention groups (mean 7.18 months in HA versus 6.82 months in PRP) minimizes potential confounding from disease duration. Bansal et al. (2021) investigated the relationship between symptom duration and therapeutic response to PRP in 206 patients with knee OA in the United States, reporting that while earlier intervention generally yielded better outcomes, PRP demonstrated efficacy across various chronicity subgroups.[13] This supports the generalizability of our findings across different disease durations.

The pathophysiological basis for the superior efficacy of PRP observed in our study likely relates to its comprehensive biological effects on the OA disease process. As reviewed by Everts et al. (2020), PRP modulates multiple pathways involved in OA pathogenesis, including inflammation, matrix degradation, and cellular dysfunction.[15] The diverse growth factors and bioactive proteins in PRP, including transforming growth factor-β, PDGF, and VEGF, stimulate chondrocyte proliferation, matrix synthesis, and anti-inflammatory effects. In contrast, HA primarily provides viscoelastic supplementation with limited biological modulation, potentially explaining the observed efficacy differential.

The long-term durability of PRP effects beyond our 3-month assessment period is supported by studies with extended follow-up durations. Di Martino et al. (2019) conducted a 5-year follow-up of a randomized controlled trial comparing PRP and HA in 192 patients with knee OA in Italy, reporting sustained superiority of PRP in pain reduction and functional improvement throughout the extended observation period.[19] This suggests that the advantage of PRP observed in our study at 3 months may potentially persist over longer timeframes.

The increasingly divergent efficacy trajectory between PRP and HA observed in our study has important implications for understanding the mechanisms of action of these interventions. The immediate post-injection benefits observed with both modalities likely reflect similar mechanisms, including dilution of inflammatory cytokines and mechanical enhancement of synovial fluid properties. However, the progressive widening of the efficacy gap over time suggests that the biological effects of PRP, including stimulation of cellular regeneration and modulation of inflammatory pathways, contribute to sustained and progressive improvement beyond the immediate mechanical effects.

Clinical Significance

Significant implications for clinical practice in conservative care of knee OA arise from the results of this randomized controlled study. Clinicians should use the evidence-based recommendations for PRP's better effectiveness over HA to help them choose the best intra-articular injection methods for patients with mild to moderate knee OA, especially when it comes to medium to long-term results.

The magnitude of improvement observed with PRP in both pain (77.8% reduction in VAS scores) and function (28.4% enhancement in WOMAC scores) at 3 months represents clinically meaningful benefits that exceed established minimal clinically important difference thresholds for OA interventions. This suggests that beyond statistical significance, PRP offers tangible improvements in patient quality of life and functional capacity that may translate to enhanced activities of daily living and reduced disability burden.

The temporal pattern of improvement observed in our study provides valuable insights for setting appropriate patient expectations regarding therapeutic trajectories. The progressive nature of improvement with PRP, with benefits continuing to accrue over the 3-month observation period, contrasts with the more modest and plateauing benefits observed with HA. This allows clinicians to counsel patients on expected outcomes and timeframes, potentially enhancing adherence to comprehensive management plans and reducing inappropriate recourse to more invasive interventions.

The comparable baseline characteristics between our intervention groups, particularly regarding age, symptom chronicity, and radiographic severity, enhance the applicability of our findings to typical clinical populations with knee OA. The inclusion of patients with common comorbidities, especially diabetes mellitus, reflects real-world clinical scenarios and suggests that the observed benefits of PRP may extend to patients with metabolic comorbidities who constitute a significant proportion of the knee OA population.

With no notable negative events in either intervention group, the safety profile often seen in the present study fits the known safety records for both IA-HA as well as IA-PRP in knee OA therapy. Reporting very minor adverse effects in this management mostly restricted to temporary local responses, Chavda et al. (2022) systematically reviewed HA for knee OA.[10] In line with this, Buontempo et al. (2023) examined PRP applications over the previous five years to validate the positive safety profile across many orthopaedic purposes.[103] For suitable people with knee OA, these reassuring safety evidence along with the benefits of PRP warrant its first-line injectable therapeutic consideration.

Integration of our results with patient-specific elements such age, comorbidity profile, illness severity, and treatment preferences might maximize therapeutic decision-making in clinical practice. The structured follow-up protocol employed in our study, with assessments at 2 weeks, 6 weeks, and 3 months, provides a practical template for post-intervention monitoring those balances comprehensive evaluation with reasonable resource utilization.

CONCLUSION

This randomized controlled trial provides compelling evidence that both IA-PRP as well as IA-HA injections effectively reduce pain along with improvement of function in patients with mild to moderate knee OA, but with significantly different efficacy profiles. While both interventions demonstrated statistically significant improvements from baseline across all assessment timepoints, PRP consistently exhibited superior clinical outcomes, particularly in the medium to long-term evaluation periods. At 3 months post-intervention, PRP demonstrated a 4.00-point reduction in VAS scores compared to 2.27 points with HA ($p<0.001$), and a 21.18-point improvement in WOMAC scores versus 6.82 points with HA ($p<0.001$). The intergroup comparative analysis revealed progressively divergent efficacy trajectories, with PRP's superiority becoming more pronounced with time. This temporal pattern suggests that PRP may facilitate sustained biological effects beyond the initial injection, consistent with its proposed mechanism of action in stimulating endogenous regenerative pathways. The comparable comorbidity profiles and OA severity distributions between groups strengthen the validity of these comparative findings. These results support the preferential use of IA-PRP over IA-HA, particularly when long-term symptomatic relief as well as improved status of function are primary therapeutic objectives.

STRENGTH OF THE STUDY

This prospective randomized controlled trial demonstrates several methodological strengths that enhance its scientific validity and clinical relevance. The study's robust design incorporates balanced intervention arms (n=22 per group) derived from appropriate power calculations, ensuring adequate statistical power to detect clinically meaningful differences. The homogeneous baseline characteristics between groups—particularly regarding age, symptom duration, and OA severity grading—minimize potential confounding variables. The implementation of validated outcome measures (VAS and WOMAC scores) at multiple pre-specified timepoints (baseline, 2 weeks, 6 weeks, and 3 months) allows for comprehensive longitudinal assessment of both symptomatic and functional parameters. The rigorous statistical methodology employing both paired and independent t-tests enables robust intragroup and intergroup comparisons. Notably, the meticulous application of established inclusion/exclusion criteria and standardized injection protocols enhances reproducibility. The study's examination of comorbidity profiles, particularly diabetes mellitus, provides valuable insights into potential interaction effects between metabolic conditions and therapeutic interventions, addressing an important clinical consideration in real-world OA management.

RECOMMENDATIONS

Future research should incorporate extended follow-up periods (minimum 12-24 months) to evaluate long-term efficacy and safety profiles of both interventions. Multicenter trials with larger sample sizes stratified by prognostic factors (age, gender, BMI, comorbidities) would enhance generalizability and enable identification of patient-specific response predictors. Implementation of double-blinding methodology and inclusion of placebo control groups would strengthen internal validity. Complementing subjective outcome measures with objective parameters (synovial fluid biomarkers, quantitative MRI, gait analysis) would provide mechanistic insights into therapeutic effects. Standardization of PRP preparation protocols (concentration, activation methods, leukocyte content) is essential for reproducibility across studies. Cost-effectiveness analyses comparing PRP versus HA would inform healthcare resource allocation decisions. Finally, investigation of combination or sequential therapy approaches may optimize therapeutic outcomes, particularly in patients with advanced disease or multiple comorbidities where monotherapy demonstrates suboptimal efficacy.

SUMMARY

This prospective RCT evaluated and compared the clinical along with status of function on using IA-PRP versus IA-HA injections in the management of mild to moderate knee OA. The investigation was conducted at R.L. Jalappa Hospital and Research Center over an 18-month period, recruiting 44 patients who were randomized into two equal intervention groups (n=22 each).

The study population demonstrated balanced baseline characteristics, with comparable age distributions (mean 54.23 years in HA group versus 52.41 years in PRP group), symptom chronicity (mean 7.18 months versus 6.82 months), and radiographic severity (86.4% KL grade II in both groups). Demographic analysis revealed a female predominance in both cohorts, though more pronounced in the HA group (72.7% versus 59.1%). Diabetes mellitus represented the most prevalent comorbidity across both intervention arms (77.3% in HA group, 68.2% in PRP group). Primary outcome measures included VAS as well as WOMAC, administered at four standardized timepoints: baseline, 2 weeks, 6 weeks, and 3 months post-intervention.

Both interventions demonstrated statistically significant improvements in pain and function from baseline at all assessment timepoints ($p<0.001$). Within the HA cohort, mean VAS scores progressively decreased from 5.05 at baseline to 2.77 at 3 months, representing a 45.1% reduction. Similarly, WOMAC scores

improved from 69.45 to 62.64, indicating a 9.8% functional enhancement. The PRP group exhibited more substantial improvements, with VAS scores decreasing from 5.14 to 1.14 (77.8% reduction) and WOMAC scores improving from 74.68 to 53.50 (28.4% enhancement) at 3 months.

Comparative analysis revealed a divergent efficacy trajectory between interventions. While baseline scores were statistically comparable between groups (p=0.305 for VAS, p=0.073 for WOMAC), the PRP group demonstrated increasingly superior outcomes at subsequent timepoints. By 2 weeks, PRP showed statistically superior pain reduction (p=0.006), with this advantage progressively increasing at 6 weeks (p<0.001) and 3 months (p<0.001). Functional improvements followed a similar pattern, with PRP demonstrating superior WOMAC scores at 3 months (p=0.002).

This temporal efficacy pattern is particularly noteworthy, suggesting that PRP may exert sustained biological activity beyond the initial injection, consistent with its proposed mechanism of action in stimulating endogenous regenerative pathways and modulating inflammatory processes. In contrast, HA primarily provides biomechanical benefits through viscoelastic supplementation, potentially explaining its more modest therapeutic effect.

The study's findings align with emerging evidence suggesting that PRP represents a superior therapeutic option for knee OA, particularly for patients seeking medium to long-term symptomatic relief as well as functional improvement.

This RCT finds that IA-PRP is more effective than IA-HA for moderate to mild knee OA and that with time the therapeutic efficacy of IA-PRP becomes more evident. These findings have significant implications for clinical practice guidelines for nonsurgical therapy of knee osteoarthritis as well as treatment algorithms development.

Fewer limitations in this study warrant consideration, including the relatively short follow-up duration, smaller study population, gender imbalance between two study groups, absence of blinding methodology, and reliance on subjective outcome measures. Future research should address these limitations through extended follow-up periods, larger multicentred trials, as well as implementation of blinding protocols, and incorporation of fewer objective outcome parameters.

LIMITATION

The relatively short follow-up duration (3 months) precludes assessment of long-term efficacy and safety profiles, particularly important when evaluating regenerative interventions like PRP that may demonstrate continued biological activity beyond the observation period. The modest sample size (n=44), while statistically adequate for primary outcomes, limits subgroup analyses that might identify patient-specific predictors of therapeutic response. The gender imbalance between groups (72.7% female in HA versus 59.1% in PRP) introduces potential bias, as gender-specific differences in OA pathophysiology are well-documented. The single-center design limits generalizability across diverse clinical settings and patient populations. Additionally, the absence of blinding in both participants and clinicians introduces potential performance and detection bias. The study's reliance on subjective outcome measures (VAS, WOMAC) without complementary objective assessments (e.g., inflammatory biomarkers, imaging parameters, or biomechanical evaluations) provides an incomplete picture of therapeutic efficacy. Finally, the lack of a placebo control group precludes determination of absolute efficacy beyond natural disease fluctuation or placebo effects.

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