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CLINICAL EFFICACY OF PLATELET-RICH PLASMA INJECTIONS IN COMMON MUSCULOSKELETAL DISORDERS

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ABSTRACT

Together osteoarthritis (OA) of the knee, epicondylitis of the elbow and tendinopathy of the shoulder rotator cuff (RC) affect 5.9% to 13.8% of the general population worldwide. These conditions cause significant disability to the general population and burden the healthcare system. Common treatments for these conditions include physical therapy (PT), pain medication, and various injection therapies. The problem with these conditions is that the damaged tissue has poor or no direct blood supply, thus, the natural healing process may become hindered and tissue becomes worn and damaged. The advancements in molecular biology have made doctors seek new methods to treat these common conditions.

Platelet-rich plasma (PRP) is a concentrate derived from whole blood and depleted of red blood cells through centrifugation. PRP is defined as a minimum of 1,000,000 platelets / microliters in a plasma solution. Platelets and this concentrate contain growth factors (GF) and other cytokines that may stimulate healing in joints and soft tissue. PRP was first utilised in veterinary medicine and dentistry, gradually finding its way to medicine. The theory is to take natural biological autologous growth factors (GF) from human blood and inject them where they would facilitate normal tissue healing. PRP's effects are complex and somewhat unknown as not all the signal pathways and interactions are known down to the finest detail.

This doctoral thesis mainly aims to 1) determine whether PRP postpones the need for knee arthroplasty in knee osteoarthritis (KOA); 2) investigate the long-term effects of PRP on the RC tendinopathy of the shoulder; 3) determine the effectiveness of PRP treatments in chronic lateral epicondylitis of the elbow; 4) study whether any subgroups of patients concerning the degree of OA or body mass index (BMI) benefit from the treatment more than other potential subgroups. This thesis is based on five retrospective studies following the aforementioned patient groups who received PRP injection treatments or conservative treatments that are widely accepted for their musculoskeletal disorder. The patients were treated at the district hospital of Forssa, in the Welfare District of Forssa.

KEYWORDS: Platelet-Rich Plasma, Osteoarthritis, Injections, Tendinopathy, Tennis Elbow

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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TIIVISTELMÄ

Polven nivelrikko, tenniskyynärpää ja olkanivelen kiertäjäkalvosimen jännerappeuma ilmenevät yhteensä noin 5.9–13.8 % väestöä maailmanlaajuisesti. Nämä tuki- ja liikuntaelinsairaudet aiheuttavat merkittävää toimintakyvyn alenemaa populaatiossa sekä kuormitusta terveydenhuollossa. Yhteistä näiden sairauksien hoidossa ovat fysioterapia, kipulääkitys ja erilaiset pistoshoidot. Yhteistä on myös sairastuneen kudoksen heikentynyt verenkierto ja kudoksen luonnollisen paranemiskyvyn heikkous, joista seuraa kudoksen kuluminen ja vaurioituminen ajan kuluessa. Molekyylibiologian edistysaskeleet ovat inspiroineet tutkijoita etsimään uusia hoitomuotoja näihin yleisiin sairauksiin.

Verihiutaleplasma on verestä valmistettu tuote, josta on poistettu punasolut sentrifugoimalla veri. Verihiutaleplasman määritelmänä pidetään vähintään 1,000,000 verihiutaletta per mikrolitra plasmavalmistetta. Plasma ja verihiutaleet sisältävät runsaasti kasvutekijöitä ja muita sytokiineja, jotka osallistuvat kudoksen paranemiseen johtavaan kaskadiin säätelemällä tulehdusta, arven muodostusta ja kudoksen uusiutumista. Verihiutaleplasmaa on käytetty aluksi eläin- ja hammaslääketieteessä, josta se on päätynyt muuhun lääketieteeseen. Teoria verihiutaleplasman tehosta perustuu ajatukseen viedä luonnolliset omasta kehosta peräisin olevat kasvutekijät alueille, joissa kudoksen paranemiskyky on heikko. Verihiutaleplasman vaikutukset ovat monimutkaisia ja osittain vielä tuntemattomia, sillä kaikkia solujen välisiä ja sisäisiä signalointi ketjuja ei vielä tunneta pienimpien yksityiskohtien tasolla.

Tämän väitöskirjan tavoitteet olivat 1) määrittää viivästyttääkö verihiutaleplasma tekonivelleikkauksen ajankohtaa polven nivelrikkopotilailla; 2) tutkia verihiutaleplasman pitkäaikaisia vaikutuksia olkapään kiertäjäkalvosimen jännerappeumissa; 3) määrittää verihiutaleplasmahoitojen tehokkuus kroonistuneessa tenniskyynärpäävaivassa; 4) selvittää vaikuttaako nivelrikon vaikeusaste tai painoindeksi hoidon tehoon. Tämä väitöskirja perustuu viiteen retrospektiivisesti tehtyyn tutkimukseen, jossa on seurattu edellä mainittuja potilasryhmiä, jotka ovat saaneet joko verihiutaleplasma hoitoja tai nykyisiä yleisesti käytettyjä ei-leikkauksellisia hoitoja. Potilaat saivat hoidot Forssan aluesairaalassa.

AVAINSANAT: Verihiutaleplasma, nivelrikko, injektiot, kiertäjäkalvosimen jännerappeuma, tenniskyynärpää

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Abbreviations

ANG-1	Angiopoietin-1
APAP	Acetaminophen
BMI	Body mass index
COX	Cyclooxygenase
COX-2	Cyclooxygenase 2
CS	Corticosteroid
CTGF	Connective tissue growth factor
DASH	Disabilities of the Arm, Shoulder, and Hand
ECGF	Endothelial cell growth factor
ECM	Extracellular matrix
EGF	Epithelial growth factor
ESWT	Extracorporeal shock wave therapy
FGF	Fibroblast growth factor
HA	Hyaluronic Acid
HGF	Hepatocyte growth factor
HOA	Hip osteoarthritis
IGF-I	insulin-like growth factor 1
IGF-II	insulin-like growth factor 2
IL-1 β	Interleukin 1 β
IL-1	Interleukin 1
IL-6	Interleukin 6
IL-7	Interleukin 7
IL-8	Interleukin 8
IL-10	Interleukin 10
KGF	Keratinocyte growth factor
K-L	Kellgren-Lawrence
KOA	Knee osteoarthritis
LP-PRP	Leukocyte-poor platelet-rich plasma
LR-PRP	Leukocyte-rich platelet-rich plasma
MCID	Minimal clinically important difference
MIP-1α	Macrophage inflammatory protein 1α

MMP	Matrix metalloproteinase
MMP 2	Matrix metalloproteinase 2
MMP 3	Matrix metalloproteinase 3
MMP 9	Matrix metalloproteinase 9
MMP 13	Matrix metalloproteinase 13
MRI	Magnetic resonance imaging
NAP-2	Neutrophil-activating protein-2
NF-κB	Nuclear factor-kappa B
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
PDGF	Platelet-derived growth factor
PF-4	Platelet factor 4
PGE2	Prostaglandin E2
PRF	Platelet-rich fibrin
PROM	Patient-reported outcome measures
PRP	Platelet-rich plasma
PRTEE	Patient-Related Tennis Elbow Evaluation
PT	Physical therapy
RC	Rotator Cuff
RCS	Rotator Cuff Syndrome
RCT	Randomised controlled trial
ROM	Range of motion
SD	Standard deviation
SDF-1α	Stromal cell-derived factor 1α
TGFβ-1	Transforming growth factor β-1
TIMP 1	Tissue inhibitor of metalloproteinase 1
TKA	Total Knee Arthroplasty
TNFα	Tumour necrosis factor-alpha
US	Ultrasonography
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WORC	Western Ontario Rotator Cuff Index

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I J. A. Annaniemi, J. Pere, S. Giordano. Platelet-rich plasma versus hyaluronic acid injections for knee osteoarthritis: a propensity-score analysis. *Scandinavian Journal of Surgery*, 2019; 108(4): 329–337.

II J. A. Annaniemi, J. Pere, S. Giordano. Platelet-rich plasma versus corticosteroid injections for rotator cuff tendinopathy: a comparative study with up to 18-month follow-up. *Clinics in Shoulder and Elbow*, 2022; 25(1): 28–35.

III J. A. Annaniemi, J. Pere, S. Giordano. Platelet-Rich Plasma Injections Decrease the Need for Any Surgical Procedure for Chronic Epicondylitis versus Conservative Treatment – A Comparative Study with Long-Term Follow-up. *Journal of Clinical Medicine*, 2022; 12(1): 102.

IV J. A. Annaniemi, J. Pere, S. Giordano. The effects of platelet-rich plasma injections in different stages of knee osteoarthritis. *European Journal of Orthopaedic Surgery & Traumatology*, 2023; 33(6): 2611–2617.

V J. A. Annaniemi, J. Pere, S. Giordano. The Efficacy of Platelet-Rich Plasma Injection Therapy in Obese versus Non-Obese Patients with Knee Osteoarthritis: A Comparative Study. Manuscript.

1 Introduction

The global prevalence of knee and hip osteoarthritis (OA) is approximately 3.75% in general population, increasing steadily over time. (Safiri et al., 2017) Rotator cuff syndrome (RCS) strongly correlates with age; the prevalence ranges from 10% to 62% from ages 20 to 80. (Teunis et al., 2014) The lateral epicondylitis of the elbow affects 1% to 3% of the general population. (Degen et al., 2018) Together, these diseases place a significant burden on the general population and healthcare providers. (Haas et al., 2018) Treatment options for knee osteoarthritis (KOA) include PT, weight loss, exercise, topical and oral non-steroid anti-inflammatory drugs (NSAIDs), intra-articular hyaluronic acid (HA) or corticosteroid (CS) injections, tibiofemoral bracing, topical capsaicin, other pain medications (acetaminophen and mild opioids such as tramadol), and of course, total knee arthroplasty (TKA). (Kolasinski et al., 2020) Historically RC tendinopathy and elbow epicondylitis have shared similar treatment options as KOA, such as PT, pain medication options, bracing, and exercise, as well as the respective anatomical locations for these diseases, which are common places for injection therapies. (Moran & Werner, 2023; Lenoir et al., 2019) Another common factor for these diseases is the importance of non-operative treatment options. (Moran & Werner, 2023; Lenoir et al., 2019; Canovas & Dagneaux, 2018; Bechay et al., 2020) Also, the dramatic increase in TKA is daunting in many ways, including the higher costs associated with surgical procedures and the inevitable increase in knee revision rates. (Stone et al., 2022; Le Stum et al., 2022) Alternative treatment options are desperately needed.

Platelet-rich plasma (PRP) is an autologous platelet concentrate, derived from whole blood via centrifugation with a concentration of at least 1,000,000 platelets/μL or approximately a 3- to 5-fold number of platelets compared to whole blood. (Marx, 2001) PRP is part of the family of platelet concentrates, which have reportedly been used in medicine since the 1970s. (Shively et al, 1966) Platelet concentrates were first used to improve healing and replace fibrin glues. (Su et al, 2022) After that, the research field expanded enormously in clinical and basic science. (Fice et al., 2019; Rodríguez-Merchán et al., 2022) In surgery field, PRP is studied and utilised in wound healing, as well as muscle, tendon, ligament, and cartilage pathology. (Fice

et al., 2019; Rodríguez-Merchán et al., 2022) PRP concentrate and the platelets contain numerous beneficial GFs, such as platelet-derived growth factor AB (PDGF-AB), transforming growth factor β-1 (TGFβ-1), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF-I and IGF-II), fibroblast growth factor (FGF), tissue inhibitor of metalloproteinase (TIMP) 1, matrix metalloproteinase (MMP) 13 and interleukins (IL) 1, 6 and 10, in high quantities. (17) In vitro studies suggest that PRP contributes to muscle and cartilage cell regeneration, decreases cartilage catabolism, and has anti-inflammatory effects. (Kunze et al, 2019)

This thesis aimed to examine the clinical effects of PRP injections in typical degenerative joint and ligament diseases. The first objective was to determine whether PRP injections would postpone the need for TKA in mild to moderate KOA. The second objective was to investigate if PRP would reduce the symptoms of RC tendinopathy. The third objective was to determine if PRP would alleviate symptoms in chronic elbow lateral epicondylitis when standard conservative treatment options have failed. The last objective was to determine if PRP has any difference in efficacy depending on the patient's BMI or the grading of the KOA. The data for the analysis was collected from the electronic patient record system of Forssa District Hospital.

2 Review of the Literature

PRP is part of the family of platelet concentrates, which have been studied since the 1950s and used in transfusion medicine since the 1960s. (Shively et al, 1966; Kingsley, 1954) Kingsley (1954) coined the the term PRP to describe platelet concentrate used for transfusions. PRP is an autologous platelet concentrate with over 1,000,000 platelets/μL, derived from whole blood via centrifugation; and the current definition is largely based on the definition in Marx's (2001) published paper. The platelet concentrations are roughly 3- to 5-fold the number of platelets compared to whole blood. (Marx, 2001) Besides platelets, the PRP concentrate contains various chemokines, cytokines, GFs, and clotting factors from the whole blood. (Alves & Grimalt, 2018) Four main types of PRP have been identified 1. leukocyte-poor PRP (LP-PRP) or pure PRP; 2. leukocyte-rich PRP (LR-PRP); 3. leukocyte-poor platelet-rich fibrin or pure platelet-rich fibrin (PRF); 4. leukocyte-rich PRF, with the main differences between the types being the number of leukocytes or the absence of fibrin structure. (Alves & Grimalt, 2018; Ehrenfest et al., 2009)

Applications in clinical medicine broadened in the 1970s and 1980s when PRP was introduced to surgical procedures as a sealant and source of transfusion to reduce intraoperative blood loss. (Mościcka & Przylipiak, 2021) PRP found its way to heart surgery, maxillofacial surgery, and dentistry by the 1990s with applications to improve transplant incorporation. (Mościcka & Przylipiak, 2021) Encouraging results in clinical and research fields pushed the PRP further into dentistry in the 2000s, leading to the invention of platelet-rich fibrin, which was widely used in dentistry for various conditions from wound closure to gingival recession. (Alves & Grimalt, 2018; Mościcka & Przylipiak, 2021)

Clinicians in the orthopaedics field showed interest in PRP, launching wider-scale growth factor studies of the tendon tissue and further leading to animal studies showing its healing effects on muscle tissue by the late 2000s. (Mościcka & Przylipiak, 2021) By this time, dermatology had begun using PRP for treating skin conditions and stimulating hair growth. (Mościcka & Przylipiak, 2021) Later, orthopaedics, plastic surgery, urology, ophthalmology, gynaecology, paediatric surgery, and other fields have used PRP for various conditions. (Alves & Grimalt, 2018) PRP has also prompted researchers to delve into the molecular biology of

various diseases which has pushed the basic level of understanding of the diseases and conditions that PRP has been used to treat. (Alves & Grimalt, 2018) Studies in orthopaedic field focus on the effects of PRP in OA, various tendinopathies, ligament injuries, and as a potential augmentation used with surgical intervention to promote post-operative healing of the surgical site. (Obana et al., 2021)

2.1 Pathogenesis of osteoarthritis

OA is the most common joint disease in the world, affecting millions of people, and is the leading cause of disability in elderly people. (Mandl, 2019; Hunter et al., 2020) OA's pathophysiology is more complex than previously thought, and all the details are yet to be discovered. (Buchanan et al., 2023) OA is an inflammatory disease with biomechanical aspects and changes occurring during the disease progression, ultimately destroying the affected joint. (Buchanan et al., 2023) Risk factors for OA have been identified, such as obesity, synovitis, diabetes mellitus, joint shape, joint malalignment or dysplasia of the joint, genetic factors, trauma, certain sports and occupations, and metabolic syndrome through low-level inflammation in the body, as well as old age or ageing and the similar low-level inflammation that develops with it. (Buchanan et al., 2023; Vina & Kwoh, 2018; Abramoff et al., 2020)

According to current literature, the cytokines primarily involved in OA are nuclear factor-kappa B (NF-κB), several MMPs (including MMP2, MMP3, MMP9, MMP13), tumour necrosis factor-alpha (TNFα), interleukin 1-beta (IL-1β), interleukin 6 (IL6), interleukin 7 (IL7), interleukin 8 (IL8), cyclooxygenases (COXs, e.g. COX-2), and prostaglandin E2 (PGE2). (Jrad et al., 2023; Mehana et al., 2019, Liu S et al., 2022) The balance in the quantity of these cytokines is crucial whether the joint is pushed into a pathologic state or remains in a homeostatic state. (Jrad et al., 2023, Mehana et al., 2019, Liu S et al., 2022) NF-κB pathway is one of the key elements in pathological as well as, normal physiological reactions of the cells in the joint, as it directly controls or impacts cell proliferation, apoptosis, cell migration, cell differentiation, and survival. (Jimi et al., 2019; Choi et al., 2019) Prolonged elevated NF-κB levels drive the chondrocytes towards catabolism, and apoptosis, and promote inflammation. (Jimi et al., 2019; Choi et al., 2019) NF-κB is activated by mechanical stress, degeneration of the extracellular matrix (ECM), and pro-inflammatory cytokines TNFα, IL1β, and IL6, which are released from damaged cartilage tissue and synovium, forming a vicious cycle and prolonged inflammatory response. (Jimi et al., 2019; Choi et al. 2019; Knights et al., 2023) NF-κB also promotes inflammatory processes in the synovial tissue of the joint, further accelerating the ongoing inflammation. (Choi et al., 2019) Chronic synovitis also speeds up the progression of OA. (Knights et al., 2023)

The ECM is the surrounding non-cellular structure, composed of several different macromolecules including collagen, elastin, and proteoglycans, upon which the cells lie. (Theocharis et al., 2016) MMPs can degrade and destroy ECM. (Mehana et al., 2019) MMP-13 has probably the most significant role in OA due to its degrading type II collagen and proteoglycan aggrecan in the cartilage ECM. (Mehana et al., 2019; Young et al., 2019) The degradation of the surrounding ECM in cartilage and bone, ultimately disrupts normal cell functions. (Choi et al., 2019; Theocharis et al., 2016; Young et al., 2019) Degradation of the ECM is an important mechanism in OA's development and progression. (Young et al., 2019) The elevated levels and production of NF-κB, COX-2, PGE2, TNFα, IL-6, and other cytokines promote the increased production of catabolic MMPs leading to cartilage degradationg. (Jrad et al., 2023; Mehana et al., 2019; Liu S et al., 2022; Jimi et al., 2019; Choi et al., 2019) Table 1 summarises the important cytokines involved in the pathogenesis of OA.

Table 1. Summary of important cytokines involved in the pathogenesis of osteoarthritis.

Cytokine	Function
nuclear factor-kappa B	Cell proliferation, apoptosis, cell migration, cell differentiation, cell survival; promotes inflammation, and the production of catabolic matrix metalloproteinases
tumour necrosis factor-alpha	Promotes inflammation and triggers the production of other pro-inflammatory cytokines, including interleukin-1 and 6
interleukin-1-beta	Promotes inflammation and catabolism and induces the production of matrix metalloproteinase 13 and other proteases
interleukin-6	Promotes inflammation and induces matrix metalloproteinases 3 and 13, leading to extracellular matrix degradation and enhancing interleukin-1-beta and tumour necrosis factor-alpha effects
interleukin-7	Increases the production of tumour necrosis factor-alpha and promotes the maturation of osteoclasts leading to bone resorption
interleukin-8	Promotes inflammation and the release of matrix metalloproteinase 13
cyclooxygenases	Produces pain and inflammation mediating prostaglandins
prostaglandin E2	Activates sensory of pain in the subchondral bone and mediates subchondral bone sclerosis
Matrix metalloproteinases	Degrades the extracellular matrix of the cartilage and bone, disrupting cell attachment

2.2 Pathogenesis of tendinopathy

Tendinopathy-related problems are increasingly more common with the ageing population and present a major clinical problem. (Korcari et al., 2023) Tendinopathy is a pathological condition of a tendon where clinical symptoms such as prolonged

pain, loss of function, and swelling occur due to the combined play of gradual degeneration due to stem cell exhaustion, mechanical stress, or injury and inflammation. (Korcari et al., 2023; Bruni et al., 2023; Griffith et al., 2022; Benage et al, 2022) Most prominent tendinopathies involve Achilles, patellar and RC tendons and the extensors of the wrist (lateral epicondylitis). (Degen et al., 2018; Griffith et al.; 2022, Maffulli et al., 2020) The mechanical stress or injury manifests as the tendon fibres become microscopically or macroscopically damaged. (Korcari et al., 2023; Benage et al., 2022) The likelihood of damage increases with ageing, overuse, denervation, and immobilisation; other risk factors include anatomical asymmetricities and obesity. (Korcari et al., 2023; Benage et al., 2022; Maffulli et al., 2020; Thampatty & Wang, 2018) Mechanical stress or injury promotes the inflammatory response as part of the natural healing process; however, the process may stray from its original purpose, becoming dysregulated and causing further damage. (Schulze-Tanzil et al., 2018)

The primary composition of the tendon tissue is collagen type I (70% of the dry weight); the remaining mass is a mix of other collagen types, proteoglycans, glycoproteins, and glycosaminoglycans. (Schulze-Tanzil et al., 2018) Tenocytes are the cellular component of tendons and are sparsely scattered within the tendinous tissue. (Schulze-Tanzil et al., 2018) The healing process in tendons includes extrinsic healing which starts the process and is overlapped by intrinsic healing. (McBeath & Chung, 2023) During the extrinsic healing process the inflammatory cells are recruited to the site of injury, followed by intrinsic healing when local stem cells begin regenerating and repairing the tissue. (McBeath & Chung, 2023; Stauber et al., 2020) Microscopical damage may accumulate over time without triggering the healing processes, and it is speculated that without extrinsic healing, the damage continues accumulating, and the tendon begins degenerating. (Stauber et al., 2020)

Mechanical stress or injuries may trigger an inflammatory response within the tendon via increased release of TNFα and interleukin 1β (IL-1β), further leading to releasing and producing proinflammatory cytokines, including MMPs. (Smith et al., 2023) IL-1β also contributes to degrading the ECM through increasing levels of prostaglandin E2 (PGE2), which sustain the inflammation. (Bergqvist et al., 2019) Some cytokines have a dualistic or somewhat balancing role in the inflammatory response, including interleukin 6 (IL-6), in which concentrations are elevated after prolonged exercise along with collagen synthesis in the peritendinous tissue. (Docherty et al., 2022; Ellis et al., 2022) Another important inflammation mediator is TNFα, which promotes an acute inflammatory response. (Ellis et al., 2022) TNFα serves as a general inflammatory mediator by increasing the production of ECM degrading enzymes, TNFα expression of the tenocytes, reducing collagen type I deposition, and increasing elastin gene expression, IL-1β expression and IL-6 expression. (Smith et al., 2023; Ellis et al., 2022) After the initial pro-inflammation

stage, the downregulation begins with IL-6 serving its dualistic role by inhibiting TNFα release, and lastly, transforming growth factor beta (TGF-β) serves as the anti-inflammatory cytokine inhibiting the production of IL-1β, TNFα, and IL-6. (Ellis et al., 2022) Over-all, the cytokine signalling and immunological responses are necessary for normal healing to occur after damage to tendons; however, the process may stray from the normal healing process or not become properly initiated, which may lead to tendinopathy and disruption of the normal tissue such as the collection of lipid deposits, calcification and microtears. (Smith et al., 2023; Bergqvist et al., 2019; Docherty et al., 2022; Ellis et al., 2022) Table 2 summarises important cytokines involved in the pathogenesis of tendinopathy.

Table 2. Summary of important cytokines involved in the pathogenesis of tendinopathy.

Cytokine	Function
tumour necrosis factor-alpha	Promotes inflammation and increases the production of enzymes that degrade extracellular matrix, reduces collagen type I deposition, interleukin-1-beta expression, and interleukin-6 expression
interleukin-1-beta	Promotes inflammation and induces the production of matrix metalloproteinases and prostaglandin E2
interleukin-6	Primarily proinflammatory cytokine but serves a dualistic role by downregulating the release of tumour necrosis factor-alpha in prolonged inflammation and increasing collagen expression
cyclooxygenases	Production of pain and inflammation mediating prostaglandins
prostaglandin E2	Mediates pain response and acute inflammation
Matrix metalloproteinases	Degrades the extracellular matrix

2.3 Biological mechanisms of platelets and platelet-rich plasma

Recent studies suggest the role of platelets goes beyond just coagulation; evidence shows they play an intricate part in initiating inflammation and enabling normal healing in the various tissue substructures. (Scully et al., 2018; Ludwig et al., 2022) Platelets contain three different types of secretory granules and several different GF, which are released when platelets become activated. (Ludwig et al., 2022) The three granule types are α-granules, γ-granules, and lysosomes. (Ludwig et al., 2022) The α-granules contain many cytokines and growth factors, including transforming growth factor beta (TGF-β), transforming growth factor beta-1 (TGF-β1), platelet-derived growth factor (PDGF), VEGF, insulin-like growth factor I (IGF-I), insulin-like growth factor II (IGF-II), epithelial growth factor (EGF), endothelial cell growth factor (ECGF), FGF, and hepatocyte growth factor (HGF). (Scully et al., 2018;

Ludwig et al., 2022; Mandel et al., 2022; Wang & Li, 2023) All these GF are crucial in the normal physiological events that occur in the human body. (Ludwig et al., 2022; Mandel et al., 2022; Wang & Li, 2023) However, GF mentioned above have thus far the most substantial mitogenic and anabolic effects of the myriad cytokines and molecules contained in the platelets and plasma, as well as inflammation regulatory functions. (Ludwig et al., 2022; Mandel et al., 2022)

The functions of the previously mentioned cytokines are: TGF-β enhances ECM synthesis; PDGF, IGF-I, IGF-II, VEGF, EGF, and ECGF increase cell proliferation; and ECGF, FGF, and VEGF promote angiogenesis. (Scully et al., 2018; Ludwig et al., 2022; Mandel et al., 2022; Wang & Li, 2023) More specifically, TGF-β1 stimulates collagen synthesis, growth inhibition, apoptosis, differentiation, and activation, as well as inhibits macrophage and lymphocyte proliferation; in turn, it stimulates mesenchymal stem cell proliferation. (Scully et al., 2018; Ludwig et al., 2022; Mandel et al., 2022; Wang & Li, 2023) IGF-I and IGF-II promote cellular growth and differentiation; when coupled with PDGF, they stimulate collagen synthesis. (Scully et al., 2018; Wang & Li, 2023) VEGF and ECGF together promote neo-angiogenesis, cell migration, and growth by targeting endothelial cells. (Scully et al., 2018) FGF targets a variety of different cells including fibroblasts, endothelial cells, smooth muscle, and blood vessels, causing cellular growth and migration and blood vessel growth. (Scully et al., 2018; Mandel et al., 2022)

PRP's anti-inflammatory properties must be addressed; as previously established, the inflammatory response gone astray is a major factor in the pathogenesis of OA and tendinopathy. (Abramoff et al., 2020; Jrad et al., 2023; Choi et al., 2019; Knights et al., 2023; Griffits et al., 2022; Stauber et al., 2020; Bergqvist et al., 2019) PRP is thought to stabilise the course of inflammation and facilitate healing by guiding or controlling the inflammatory response. (Everts et al., 2023) The complex interaction of the cytokines and GF involved leads to inhibiting NF-κB signalling and chondrocyte apoptosis. (Everts et al., 2023; Li M. et al., 2022) Apoptosis is reduced in a dose-dependent manner, with higher doses of PRP reducing the apoptosis in greater proportions. (Xie et al., 2022) As discussed, tendinopathic tissue has various defects and degenerative changes, including decreased collagen content and increased expression of MMPs, microtears, and inflammatory response. (Bruni et al., 2023; Smith et al., 2023; Ellis et al., 2022) PRP induces the proliferation of tenocytes and tendon stem cells (TSC) in diseased or degenerated tendon tissue. (Chalidis et al., 2023, Liu X et al., 2022, Pauly et al., 2018, Yoon et al., 2018) In addition to cell proliferation collagen type I and type III gene expression was enhanced, and the ratio between the two types shifted towards a higher amount of collagen type I which is a more physiological state than collagen type III dominant composition. (Chalidis et al., 2023) PRP seems to act as an inflammatory mediator in damaged tendon tissue shortly promoting inflammation to

initiate the healing cascade and then guiding the healing of the tendon towards a more normal tendon structure concerning collagen type deposition, tensile strength, and overall collagen organisation and composition. (Chalidis et al., 2023; Liu X et al., 2022) Tables 1 and 2 list a summary of cytokines and GF found in PRP and platelets; Everts et al. (2020) and Everts et al. (2023) reported the same contents.

Table 3. Cytokines found in PRP and platelet α-granules and their functions.

Platelet cytokines	Functions
IL-1	Modulates the systemic inflammation; Innate immune process regulator; potent regulator of cartilage cell function
IL-6	Promotes pro-inflammation and anti-inflammation, contributes to osteoclast formation; activates innate and adaptive immunity
IL-8	Promotes pro-inflammatory activity; recruits neutrophils; induces chemotaxis; releases lysosomal enzymes; promotes angiogenesis
PF-4	Regulates leukocytes activation; has antiangiogenetic properties
B-Thromboglobulin	Stimulates mitogenesis and ECM synthesis; activates plasminogen; fibroblast synthesis; regulates platelet production
MIP-1A	Regulates inflammatory functions and immune regulation; stimulates bone remodelling; generates reactive oxygen species; stimulates leukocyte migration
NAP-2	Causes neutrophil degranulation; attracts neutrophils
SDF-1A	Calls CD34+ cells and induces their homing, proliferation, and differentiation into endothelial progenitor cells stimulating angiogenesis; calls mesenchymal stem cells and leukocytes
TNF	Regulates monocyte migration, fibroblast proliferation, macrophage activation, angiogenesis

Modified table by Everts P. et al, (2020) and Everts P. et al., (2023). Abbreviations: IL-1: Interleukin 1; IL-6: Interleukin 6; IL-8: Interleukin 8; PF-4: Platelet factor 4; MIP-1α: Macrophage inflammatory protein 1α; NAP-2: Neutrophil-activating protein-2; SDF-1α: Stromal cell-derived factor 1α; TNF: Tumour necrosis factor.

Table 4. GF and cytokines present in PRP and platelets.

Platelet growth factors	Cell sources	Functions and effects
PDGF (AA-BB-AB isomers)	Platelets, endothelial cells, macrophages, smooth muscle cells	Promotes mitogenesis of mesenchymal cells and osteoblasts; stimulates chemotaxis and mitogenesis in fibroblast/ glial/smooth muscle cells; regulates collagenase secretion and collagen synthesis; stimulates macrophage and neutrophil chemotaxis; regulates collagenase secretion and synthesis
TGF (A-B)	Macrophages, T lymphocytes, keratinocytes	Stimulates undifferentiated mesenchymal cell proliferation; regulates endothelial, fibroblastic, and osteoblastic mitogenesis; regulates collagen synthesis and collagenase secretion; regulates mitogenic effects of other growth factors; stimulates endothelial chemotaxis and angiogenesis; inhibits macrophage and lymphocyte proliferation
VEGF	Platelets, macrophages, keratinocytes, endothelial cells	Increases angiogenesis and vessel permeability; stimulates mitogenesis for endothelial cells; induces lymph-angiogenesis; induces antiapoptotic effect for endothelial cells; promotor of cell migration
EGF	Platelets, macrophages, monocytes	Induces proliferation in keratinocytes and fibroblasts; stimulates mitogenesis for endothelial cells
(A-B)-FGF	Platelets, macrophages, mesenchymal cells, chondrocytes, osteoblasts	Promotes growth and differentiation of chondrocytes and osteoblasts; promotes mitogenesis in mesenchymal cells, chondrocytes, and osteoblasts
CTGF	Platelets, fibroblasts	Promotes angiogenesis, cartilage regeneration, fibrosis, and platelet adhesion; stimulates angiogenesis; promotes connective tissue production and ECM remodelling
IGF-1	Platelets, plasma, epithelial cells, endothelial cells, fibroblasts, osteoblasts, bone matrix	Induces chemotaxis for fibroblasts and stimulates protein synthesis; enhances bone formation by proliferation and differentiation of osteoblasts; supports local tissue healing; amplifies platelet response
HGF	Platelets, mesenchymal cells	Regulates cell growth and motility in epithelial/endothelial cells, supporting epithelial repair and neovascularisation during wound healing; stimulates mitogenesis and angiogenesis
KGF	Fibroblasts, mesenchymal cells	Regulates epithelial migration and proliferation
ANG-1	Platelets, neutrophils	Induces angiogenesis stimulating migration and proliferation of endothelial cells; supports and stabilises blood vessel development via recruiting pericyte

Modified table by Everts et al. (2020) and Everts et al. (2023). Abbreviations: PDGF: platelet-derived growth factors; TGF: transforming growth factor; VEGF: vascular endothelial growth factor; EGF: epidermal growth factor; FGF: fibroblast growth factor; CTCG: connective tissue growth factor; IGF: insulin-like growth factor; HGF: hepatocyte growth factor; KGF: keratinocyte growth factor; Ang-1: angiopoietin-1; ECM: extracellular matrix.

Leukocyte-rich-PRP (LR-PRP) and leukocyte-poor-PRP (LP-PRP) may have differences in efficacy in tendinopathy and KOA based on the basic science and animal studies and meta-analyses of clinical studies. (Jayaram et al., 2023; Jiang et al., 2020; Shim et al., 2022; Abbas et al., 2022; Muthu et al., 2021) Neutrophils are associated with catabolic events such as collagen and ECM degradation; therefore, logic in basic science is to reduce their numbers to avoid an unwanted course of healing. (Shim et al., 2022) In turn, monocytes promote healing; removing most of the leukocytes from the final product decreases both cell lines. (Shim et al., 2022) The difference in efficacy between LP-PRP and LR-PRP is not found in clinical trials of KOA patients; however, the basic science suggests LR-PRP may be slightly more pro-inflammatory than LP-PRP, but the relevant connection to any different clinical outcomes is not shown, although LP-PRP is favoured over LR-PRP in KOA. (Jayaram et al., 2023; Muthu et al., 2021) In tendinopathy, the literature suggests LR-PRP would have greater efficacy than LP-PRP. However, this is also under debate because most of the studies have shown no relevant clinical differences in patient-related outcome measures (PROM) for lateral epicondylitis. (Muthu et al., 2021; Li S. et al., 2022) Whether decreased catabolism over increased anabolism is more efficient in terms of keeping or discarding the leukocytes to achieve maximal tissue healing is unclear. (Shim et al., 2022) One suggested reason for the previous difference in results between LP-PRP and LR-PRP is the requirement of inflammatory response in tendons to facilitate healing, unlike in KOA where reducing inflammation may be key to stopping the vicious cycle. (Shim et al., 2022, Muthu et al., 2021)

2.4 Clinical studies of the efficacy of platelet-rich plasma

Musculoskeletal disorders of the knee, shoulder, and elbow are the most common reasons for PRP injection therapies. (Magruder et al., 2023) The degenerative nature of the disorders included in those regions has prompted scientists to explore new and effective non-operative treatments, as surgical interventions are no longer viable or recommended - as is the case for degenerative rotator cuff disease and elbow epicondylitis, or are expensive but reserved as the absolute end-point of the disease as in KOA. (Karjalainen & Buchbinder., 2023; Hardy et al., 2021; Garibaldi et al., 2021; Kolasinski et al., 2020) The literature surrounding PRP in treating KOA, elbow epicondylitis, and degenerative RCS is diverse and heterogeneous, even conflicting, and there are no definitive literature-based indications for PRP use in KOA, elbow epicondylitis or rotator cuff disease. (Costa et al., 2023; Karim et al., 2023; Rosso et al., 2023; Linnanmäki et al., 2020; Wong et al., 2022; Liu W-C et al., 2022; Karjalainen & Buchbinder, 2023; Karjalainen T. et al., 2022)

2.4.1 Knee osteoarthritis and platelet-rich plasma

The first documentation of KOA treatment (excluding combination of PRP with some other confounding treatment or surgery) with intraarticular PRP injection according to a literature search was by Saito et al. (2009), when they treated osteoarthritic rabbit knees with autologous PRP and reported that PRP morphologically and histologically supressed OA's progression. First human trials (again excluding confounding co-existing treatments in the research setup) were conducted by Kon E et al. (2010) and Filardo G et al. (2011) when they treated patients with OA and degenerative cartilage lesions with remarkable results. Table 5 summarises the most relevant studies in terms of level of evidence and their results regarding KOA.

PRP's efficacy in treating mild to moderate KOA (K-L 1 to 3) is still under heavy debate, and whether PRP injections are better than any other treatment or placebo is unclear. (Lin et al., 2019; Di Martino et al., 2019; Louis et al., 2018; Dório et al., 2021; Yurtbay et al., 2021; Han et al., 2021; Bennell et al., 2021; Filardo G. et al., 2020; Migliorini et al., 2021; Lewis et al., 2022; Saraf et al., 2022; Tschopp et al., 2023; Elik et al., 2020; Wu et al., 2018) Several high-quality studies have depicted PRP as superior to placebo. (Lin et al., 2019; Yurtbay et al., 2021; Filardo et al., 2020; Migliorini et al., 2021; Saraf et al., 2022; Elik et al., 2020; Wu et al., 2018) Equally high-quality studies state that PRP's effects remain within the boundaries of the placebo effect, while some suggest PRP is better than a placebo but inferior to several other injection treatments. (Dório et al., 2021; Han et al., 2021; Bennell et al., 2021; Lewis et al., 2022; Tschopp et al., 2023) Several studies indicate that PRP is equal to or better than HA in mild to moderate (K-L 1-3) KOA up to 12 to 24 months with a lower reintervention rate and a lower risk of arthroplasty. (Lin et al., 2019; Di Martino et al., 2019; Han et al., 2021; Migliorini et al., 2021; Li S et al., 2023; Belk J W et al., 2023; Belk W J et al., 2021) Compared to CS injections, PRP also seems to be equal or superior, but a definitive difference in overall efficacy has not been detected, as the CS have more immediate short-term effects from 6 to 26 weeks; in contrast, PRP effects are usually seen slightly overlapping with CS effects after 3 months but lasting longer than CS. (Han et al., 2021; Migliorini et al., 2021; Lewis et al., 2022; Saraf et al., 2022; Idres & Samaan, 2023; McLarnon & Heron, 2021) PRP's effects in advanced KOA have been short-termed, but comprehensive research is missing due to most of the studies excluding end-stage KOA. (Saraf et al., 2022; Jubert et al., 2017; Vilchez-Cavazos et al., 2023) Effects of PRP treatments are usually seen later in follow-up points between 3 to 12 months, and overall beneficial effects seem to last longer than effects of CS or HA. (Di Martino et al., 2019; Migliorini et al., 2021; Li S et al., 2023; Belk J W et al., 2023; Belk J W et al., 2021; Idres & Samaan, 2023; McLarnon & Heron, 2021)

Improvements in patient-reported outcome measures (PROM), especially scores detecting pain, are usually seen between 3 to 12 months with PRP treatments, sometimes lasting up to 24 months; however, some studies suggest the improvement is no greater than a placebo can achieve. (Kon et al., 2010; Filardo et al., 2011; Lin et al., 2019; Di Martino et al., 2019; Louis et al., 2018; Dório et al., 2021; Yurtbay et al., 2021; Han et al., 2021; Bennell et al., 2021; Filardo G. et al., 2020; Migliorini et al., 2021; Lewis et al., 2022; Saraf et al., 2022; Tschopp et al., 2023; Elik et al., 2020; Wu et al., 2018; Li S et al., 2023; Belk J W et al., 2023; Belk J W et al., 2021; Idres & Samaan, 2023; McLarnon & Heron, 2021; Jubert et al., 2017; Vilchez-Cavazos et al., 2023) Some emerging evidence shows that intra-articular PRP injections would delay the need for knee arthroplasty - a similar retrospective result found in intra-articular HA injections; however, comprehensive definitive data is still missing. (Berkani et al., 2022; Cheeva-Akrapan & Turajane, 2023; Sánchez et al., 2021) The median duration of the PRP injection series is 12 months, compared to the 9 month median of HA injections, but effects may begin to diminish as early as 6 months for both treatments; however, some PRP-treated patients may have beneficial effects for over a year. (Lin et al., 2019; Di Martino et al., 2019; Yurtbay et al., 2021; Migliorini et al., 2021; Li S et al., 2023) PRP has dose dependency with two or three injections having significantly better results beyond 6 months in PROMs than a single injection but no difference in the early follow-up. (Yurtbay et al., 2021; Vilchez-Cavazos et al., 2019) Bone marrow aspirate concentrate injections showed similar PROM results compared to PRP in the 12-month follow-up with no difference between treatments. (Belk J W et al., 2023; Anz et al., 2020) PRP was superior to oral pain medications, although relatively few studies compare PRP to oral medications. (Simental-Mendía et al., 2016) Single or multiple PRP injections may offer similar or greater efficacy compared to conventional injection therapies for up to 12 months in mild to moderate KOA and perhaps for a shorter time in advanced KOA; however, according to current literature, no definitive comparison to oral pain medication exists. (Lin et al., 2019; Yurtbay et al., 2021; Han et al., 2021; Migliorini et al., 2021; Lewis et al., 2022; Saraf et al., 2022; Idres & Samaan, 2023; McLarnon & Heron, 2021, Simental-Mendía et al., 2016) Regarding intra-articular biology and inflammation markers, KOA patients treated with PRP showed decreased TNF-α and IL-1β levels in synovial fluid compared to saline-treated patients. (Chu et al., 2022) Studies on tibiofemoral cartilage volume with magnetic resonance imaging (MRI) are conflicting, with some showing that KOA patients treated with PRP showed significantly decreased loss of cartilage thickness over 60 months of follow-up versus those treated with saline, while others report no significant changes or signs of regeneration in cartilage after PRP treatments. (Chu et al., 2022; Sax et al., 2022; Raeissadat et al., 2020)

Leukocytes in the PRP solution are probably insignificant concerning clinical results, as LP-PRP and LR-PRP have demonstrated similar results in clinical KOA trials; perhaps LP-PRP has a slight edge over LR-PRP in functional recovery. (Abbas et al., 2022; Belk J W et al., 2021; Chen L et al., 2023; Di Martino A. et al., 2022) Direct comparison between LP-PRP and LR-PRP showed no statistical or clinical differences. (Chen L et al., 2023) Issues with the current PRP studies involving KOA are lack of standardisation in methodology, different PRP formulas, sometimes short follow-ups, lack of a routine double-blind or randomised controlled trial (RCT) setting, and lack of treatment failure documentation (surgery). (Costa et al., 2023) No clinical recommendations for using or avoiding PRP in clinical practice can be made as the general quality of the studies is too low for such recommendations. (Costa et al., 2023) PRP injections are safe and only mild adverse effects were reported such as post-injection pain or mild swelling, which are comparable to the adverse effects of placebo. (Costa et al., 2023; Hong M. et al., 2021)

Questions for future studies that arise are; the accumulation of sufficient placebo-controlled RCT studies to definitively answer to the matter of efficacy versus placebo and PRP efficacy compared to oral medication; Do PRP injections delay the need for arthroplasty? What are the long-term effects (if any) of repeated PRP treatment cycles in mild to moderate KOA with respect to delaying the progression of OA or controlling the symptoms?

Table 5. The most relevant comparative studies in clinical efficacy of PRP in KOA, based on study hierarchy.

Original article	Patients and KOA stage	Study setting	Outcomes and results	PRP effect (positive +, uncertain +/-, no effect -)
Lin, K-Y., *et al.* (2019).	53 patients (87 knees), Ahlbäck grade 1 to 3	RCT, placebo-controlled, double-blind study. PRP vs HA vs NS. Follow-up 12 months (1, 2, 6 and 12 months)	Primary outcome WOMAC and secondary outcome IKDC. PRP group had superior WOMAC vs HA and NS at all follow-up points after 1 month, while HA and NS had no significant differences. PRP group had significantly better IKDC scores after 1 month vs HA and NS.	+
Di Martino, A. *et al.* (2019).	192 patients, final analysis 167 patients, K-L 1 to 3	RCT, double-blind (up to 1 year), 5-year results (2, 6, 12, 24 and 64 months), PRP vs HA.	Primary outcome IKDC and secondary outcomes EQ-VAS and Tegner score. There were no differences in the clinical scores between the groups at any follow-up point. Both groups experienced improvement from baseline for up to 24 months. The median beneficial duration of PRP was 12 months; for HA it was 9 months.	+/- (PRP vs HA, no difference)
Di Martino, A. *et al.* (2022).	192 patients, K-L 1 to 3	RCT, double-blind study, LP-PRP vs LR-PRP. Follow-up 12 months (2, 6 and 12 months).	Primary outcome measure IKDC and secondary outcome measures KOOS, EQ-VAS, Tegner scale and patient judgement of the treatment experience. No differences in any of the outcome scores were detected between the groups. MCID was achieved at 6 and 12 months for IKDC, KOOS ADL, KOOS pain, KOOS QoL, KOOS sport/recreation and KOOS symptoms.	+ (PRP types compared to each other)
Dório, M., *et al.* (2021).	62 patients, K-L 2 to 3	RCT, double-blind, placebo-controlled study. PRP vs plasma vs NS. Follow-up 24 weeks (6, 12 and 24 weeks), LP-PRP and leukocyte poor plasma	Primary outcome measure VAS for pain and secondary outcome measures were WOMAC, KOOS, 5-point Likert, TUGT, analgesic consumption and self-report diary. No differences between the groups at 6 and 12 weeks in VAS. PRP group had higher Likert scores at 12 weeks over other groups and better improvement in KOOS Sport/Recreation score at 6 and 12 weeks than the plasma group. There were no clear differences in the PRP group compared to the placebo during the 24 weeks of follow-up.	- (No difference to placebo)
Yurtbay, *et al.* (2021).	237 patients, K-L 1 to 3	RCT, double-blind, placebo-controlled study. Follow-up 24 months (1, 3, 6, 12 and 24 months). Single dose LR-PRP vs single dose NS vs 3 doses PRP vs 3 doses NS.	Primary outcome measure KOOS and secondary outcome measures Kujala Patellofemoral Score, ADL, ROM, and VAS for pain. PRP groups had better VAS and KOOS at 3, 6 and 12 months than NS groups. Three doses of the PRP group had better VAS than a single dose PRP group at 12 months and better KOOS at 6 and 12 months. No differences among any of the groups were found in VAS at 24 months. Both PRP dosages were superior to placebo.	+ (Single dose and 3 doses of PRP were superior to placebo)

Bennell, K. L. *Et al*. (2021).	288 patients, K-L 2 to 3	RCT, placebo-controlled, triple-blind study. Follow-up 12 months (2 months and 12 months), 3 injections of LP-PRP vs NS	Primary outcomes were a 12-month change in overall knee pain scores (11-point numerical rating scale from 0 to 10 pain) and a percentage change in medial tibial cartilage volume in MRI. Secondary outcomes included 31 assessments for pain, function, quality of life etc. There is no between the groups in primary outcome measures and in most secondary outcome measures. PRP was not superior to placebo.	-
Lewis, E. *et al*. (2022).	102 patients, early KOA, if plain X-ray did not show KOA, then MRI was performed to confirm the diagnosis	RCT, double-blind, placebo-controlled study. Single NS vs single PRP injection + 2 NS vs 3 PRP injections. Follow-up 12 months (6 weeks, 3 months, 6 months, 12 months).	Primary outcome measures were KOOS and EQ-5D-5L. Secondary outcome measures were VAS for pain and subjective patient assessment. PRP was not superior to placebo in single or multiple injection settings in any of the primary or secondary outcomes.	- (Single or multiple PRP injections were not superior to placebo)
Saraf, A., *et al*. (2022).	90 patients, (final follow-up included 84), K-L 4 patients only	Prospective, single-blind, placebo-controlled study. Follow-up 6 months (3 and 6 months). 3 injections of LR-PRP vs 3 injections of NS (1 month interval).	Primary outcome measures were VAS for pain and WOMAC. PRP groups had greater improvement in WOMAC and VAS at 3 and 6 months compared to the placebo group.	+
Tschopp, M. *et al*. (2023).	95 patients (120 knees), K-L 1 to 3	RCT, placebo-controlled, double-blind study. Follow-up 6 months. CS vs HA vs PRP vs placebo.	Primary outcome measure NRS for pain. Secondary outcome measures WOMAC, Tegner Activity Scale, knee mobility and adverse events. No significant differences were found between the groups in pain relief, WOMAC, the Tegner score, adverse events, or knee mobility. None of the injection therapies were superior to placebo.	- (PRP was not superior to placebo or CS)
Elik, H. *et al*. (2020).	60 patients, (final analysis 57 patients), K-L 1 to 3	RCT, double-blind, placebo-controlled study. 3 injections of LR-PRP vs single injection of placebo. Follow-up 6 months (1 month and 6 months).	Primary outcome measure was VAS for pain. Secondary outcome measures were WOMAC and SF-36. PRP group was superior to placebo concerning VAS for pain at 1 and 6 months as well as for all WOMAC subscores. Most subscores of SF-36 favoured PRP over placebo at 1 and 6 months.	+
Wu, Y-T., *et al*. (2018).	20 patients (40 knees, bilateral KOA), Ahlbäck grade 1 to 2	RCT, double-blinded, placebo-controlled. Patients with bilateral KOA received single injections of LR-PRP or NS. Follow-up was 6 months (2 weeks, 1 month, 3 months and 6 months)	Primary outcome measure was WOMAC. Secondary outcome measure was isokinetic test results. PRP group showed significantly better reduction in WOMAC scores compared to the NS group. Both groups showed improvement in their respective baseline WOMAC scores. No differences were detected in muscle strength.	+

Jubert, N. J., *et al.* (2017).	75 patients (final analysis 64 patients), K-L grade 3 to 4	RCT, double-blind, parallel group study. Patients waiting for knee arthroplasty received LP-PRP or CS injections to their knee. Follow-up was 6 months (1, 3 and 6 months).	Primary outcome measure was VAS for pain at 1 month of follow-up. Secondary outcome measures were VAS, KOOS, SF-36, and patient satisfaction. PRP group did not have statistically significant differences in any of the primary or secondary outcome measures vs CS group. Both treatments improved the baseline scores but PRP had a higher absolute reduction in symptoms than the CS group at 3 and 6 months. Single injection or LP-PRP had similar effects to a single CS injection in late-stage KOA.	+/- (PRP had similar effects to CS injection)
Chu, J. *et al.* (2022).	644 patients (final analysis 610 patients), K-L grade 1 to 3	RCT, double-blind, parallel-group, multi-centre, placebo-controlled study. Blinding was up to 2 years. Patients received LP-PRP or NS. Follow-up was 60 months (3, 6, 12, 24 and 60 months).	Primary outcome measure was WOMAC. Secondary outcome measures were IKDC, VAS for pain, intra-articular biochemical markers (IL-1β and TNFα), and cartilage thickness in MRI. PRP group had significantly better results in all the clinical outcome measures (WOMAC, and all the WOMAC subscores, IKDC and VAS for pain) at 3, 6, 12, 24, and 60 months of follow-up points than the NS group. PRP's effects remained significant compared to baseline for up to 24 months. Tibiofemoral cartilage thickness decreased twice as much in NS group vs PRP group, with a substantial difference at 60 months.	+
Raeissadat, S. A. *et al.* (2020).	23 patients (46 knees, final analysis 42 knees), K-L grade 1 to 3	RCT, double-blind, bilateral KOA. Patients were randomised to the exercise group vs PRP group with the same exercise program but received an LR-PRP injection. MRI scans were performed 10-14 days before and 8 months after the intervention.	Outcome measures were WOMAC, VAS for pain, patellofemoral cartilage volume in MRI, medial and lateral meniscal disintegrity in MRI and synovitis in MRI. PRP group had significantly lower WOMAC and VAS scores at 8 months vs the exercise group. MRI showed that the PRP group also had significantly greater patellofemoral cartilage thickness and less synovitis than the exercise group at 8 months. Other outcome measures were non-significant between the groups.	+

Abbreviations: KOA: Knee osteoarthritis; RCT: Randomised controlled trial; K-L: Kellgren-Lawrence grading; PRP: Platelet-rich plasma; HA: Hyaluronic acid; NS: Normal saline; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; IKDC: International Knee Documentations Committee subjective score; CS: Corticosteroid, EQ-VAS: EuroQol Visual Analogue Scale; MCID: Minimal clinically important difference; LR-PRP: Leukocyte-rich platelet-rich plasma; LP-PRP: Leukocyte-poor platelet-rich plasma; KOOS: Knee Injury and Osteoarthritis Result Score; TUGT: Timed up and go test; ROM: Range of Motion; MRI: Magnetic resonance imaging; ADL: Activities of daily living; EQ-5D-5L: EuroQol five-dimension five-level index; NRS: Numeric rating scale; SF-36: Short-Form-36; IL-1β: Interleukin-1-beta; TNFα: Tumour necrosis factor alpha.

2.4.2 Efficacy of platelet-rich plasma in rotator cuff tendinopathy

RCS is an umbrella term covering various pathological findings in the shoulder area including tendinopathy; overall, it is a degenerative process that leads to eventual tendon wearing and finally tearing in a somewhat similar fashion as cartilage thins, eventually grinding away in end-stage OA. (Adra et al., 2023) Many different pathological or degenerative findings in magnetic resonance imaging (MRI) raise concerns about which primarily causes the symptoms. (Ashir et al., 2020) With the revolution of molecular medicine and chemistry, the properties of different cytokines and GF began revealing their potential; thus, the RC problems of the shoulder attracted attention with animal studies paving the way to human trials. (Rodeo et al., 2007) After that, several human trials followed with controversial and sometimes contradicting results. (Scarpone et al., 2013; Kesikburun et al., 2013; Hurley et al., 2019; Lee et al., 2019; Kim et al., 2019; Kwong et al., 2020; De Sanctis et al., 2020; Barreto et al., 2019) Table 6 summarises the most important original PRP studies on RCS based on their level of evidence.

PRP studies on RCS face similar issues as KOA studies, so their efficacy compared to other injection treatments, other conservative treatments, and placebo is unclear, even with the most recent meta-analyses reaching different conclusions. (Karim et al., 2023; Rosso et al., 2023; Jiang et al., 2023; Rossi et al., 2023; Peng et al., 2023; Tanpowpong et al., 2023; Feltri et al., 2023; Adra et al., 2023; Pang et al., 2023; Zhang et al., 2022) In the light of current literature, PRP was not better than placebo in RC tendinopathy in the short or long term. (Karim et al., 2023; Rosso et al., 2023) PRP and CS produce similar results in the clinical and functional improvement of partial tears and tendinopathy of RC, but conflicting evidence on whether CS are superior in the early follow-up or if PRP is better in the mid- or long-term follow-up. (Kwong et al., 2020; Rosso et al., 2023; Jiang et al., 2023; Peng et al., 2023; Adra et al., 2023) HA injections for RCS have comparable effects to PRP and CS treatments, but the results are mostly seen in the early follow-up and diminish quickly after that, resulting in PRP having better results than HA in mid- to long-term follow-up. (Jiang et al., 2023) Compared to PT or exercise programs PRP may be less effective than exercise program training in subacromial impingement syndrome in 6 months of follow-up but studies comparing the two treatments are scarce and the matter requires more research, especially on RC tendinopathy, before any further conclusion may be drawn. (Rosso et al., 2023; Jiang et al., 2023)

PRP may prevent an RC tear from progressing, cause a minor local tissue regeneration, and prevent retear after arthroscopic repair, although the clinical relevance of this finding is not studied in the long-term so the overall benefit in clinical practice is unclear. (Tanpowpong et al., 2023; Feltri et al., 2023; Zhang et al., 2022) Encouraging results of PRP treatments are found in treating adhesive

capsulitis and medium to large tear repairs of the RC, with Swiss Orthopaedics Shoulder Elbow and Expert Group even recommending the use of PRP in treating both the conditions. (Rosso et al., 2023) The progression stage of the RC tendinopathy may affect PRP injection's efficacy as subacromial PRP injections seemingly produce better results in tendinopathy without tears versus degenerative partial RC tears, with a speculated mechanism of affecting the progression of tendon pathology via growth factors and leukocyte initiated normal healing. (Rossi et al., 2023) Regarding clinical improvement, PRP seemingly reduces pain, improves ROM, and increases physical activity. (Rosso et al., 2023; Peng et al., 2023; Pang et al., 2023)

More minor adverse events, such as pain at the injection site and even a frozen shoulder, have been reported with PRP injections compared to placebo, although no major adverse events have been reported and the overall safety of PRP injections is high. (Rosso et al., 2023, Jiang et al., 2023, Rossi et al., 2023) CS injections are not without safety issues, as studies have shown that on molecular and cellular levels CS decrease suture anchor pull-out strength, maximal load to failure strength, increase tendon stiffness, decrease ECM composition, cellular proliferation, inflammation pathways activation, cellular viability, and in addition increase apoptosis and adipocyte differentiation, ultimately correlating with an increased risk of revision surgery after RC tendon repair, in a dose- and frequency-dependent manner if CS injection is given up to 6 months before surgery. (Puzzitiello et al., 2020; Hurley et al., 2019) HA injections may be safer than CS injections and be as safe as PRP injections. (Rosso et al., 2023; Jiang et al., 2023; Puzzitiello et al., 2020; Hurley et al., 2019)

Table 6. The most relevant comparative studies of the clinical efficacy of PRP in RCS, based on study hierarchy.

Original article	Patients	Study setting	RC diagnosis	Outcome and primary results	PRP effect (positive +, uncertain +/-, no effect -)
Scarpone, M. *et al*. (2013)	18 patients (19 shoulders)	Prospective, open-label study. Patients received single US-guided injections of PRP at the tendinopathy lesion or surrounding tendon after failed conservative treatment. Follow-up was 12 months (8 weeks, 12 weeks, 52 weeks).	RC tendinopathy with or without associated local tear/lesion (ranging from mild tendinopathy to a full thickness tear); MRI confirmed.	Primary outcome measure was VAS for pain. Secondary outcome measures were RC strength and endurance (8 and 12 weeks), severity of the lesion in MRI (4 and 8 weeks), and patients' satisfaction at 52 weeks. Patients were compared to their own baseline and showed significant improvement in VAS for pain, side-lying external rotation, drop arm, full can, Thera-Band external rotation at 0 and 90 degree tests. MRI severity score improved in all but 2 patients.	+/- (Lack of control group)
Kesikburun, S. *et al*. (2013)	40 patients	RCT, double-blind, placebo-controlled study. Patients received single US-guided subacromial injections of an LP-PRP or placebo. Follow-up was 12 months (3 weeks, 6 weeks, 12 weeks, 24 weeks, and 52 weeks).	Chronic RC tendinopathy without a full thickness tear; MRI confirmed.	Primary outcome measure was WORC. Secondary outcome measures were SPADI, VAS for pain in the Neer test, and shoulder ROM. Single injections of PRP were not better than placebo in any of the outcome measures.	-
Lee, H-W., *et al*. (2019)	60 patients	Case-control series. Patients received US-guided injections of LP-PRP or LR-PRP into the lesion areas of the RC or only exercise training. Follow-up was 6 months (3 and 6 months).	RC tendinopathy in MRI or US without a cuff tear.	Outcome measures were NRS for pain, ASES score, and Constant-Murley score. Both LR-PRP and LP-PRP groups had a significantly greater reduction in ASES compared to the exercise only group at 3 months. There were no intergroup differences between the PRP types.	+/- (Non-randomised study)
Kim, S., *et al*. (2019)	30 patients	Case-control study. Patients received PRP or PT/exercise training. Follow-up was 24 weeks (6, 12, 24 weeks).	RC tendinopathy, US confirmed	Outcome measures were ASES, Constant-Murley Score, and NRS for pain. Growth factor analysis was compared to clinical scores. PRP group had significantly better ASES and Constant-Murley scores at 24 weeks than the exercise group. NRS was substantially lower in the PRP group at 6 weeks than in the exercise group. TGFβ-1 and IL-	+/- (Non-randomised study)

				1β levels were related to improving the ASES and Constant-Murley score.	
Kwong, C., *et al*. (2020)	99 patients	RCT, double-blind study. Patients received a US-guided LP-PRP injection to the lesion site or CS injection to a subacromial bursa. Follow-up was 12 months (6 weeks, 3 months, 12 months).	RC tendinopathy with partial thickness tear; MRI or US confirmed.	Primary outcome measure was VAS for pain. Secondary outcome measures were ASES and WORC. PRP group had significantly better primary and secondary outcome scores at 3 months, but not after that. Both groups showed a decrease in all the scores, but the benefits diminished at 12 months without sustained benefits beyond short-term follow-up.	+/- (PRP had similar effects to CS injection)
Barreto, R B, *et al*. (2019)	51 patients	RCT, double-blind study. Patients with RC impingement syndrome received a PRP or CS injection into a subacromial space. Follow-up was 6 months (1, 3 and 6 months).	Positive Neer Impingement Test for RC impingement syndrome and no complete rupture of RC in US.	Outcome measures were the UCLA Shoulder Score, Constant-Murley Score and DASH. No differences were detected between the groups in any of the follow-up points. Both groups experienced a similar decrease in symptom scores.	+/- (PRP had similar effects to CS injection)

Abbreviations: US: Ultrasonography; RC: Rotator cuff; VAS: Visual Analogue Scale; MRI: Magnetic resonance imaging; RCT: Randomised controlled trial; WORC: Western Ontario Rotator Cuff Index; SPADI: Shoulder Pain and Disability Index; ROM: Range of motion; CS: corticosteroid, ASES: American Shoulder and Elbow Surgeons score; NRS: Numerical Rating Scale; DASH: Disabilities of the Arm, Shoulder and Hand; LR-PRP: Leukocyte-rich platelet-rich plasma; LP-PRP: Leukocyte-poor platelet-rich plasma; UCLA: University of California Los Angeles Shoulder Rating Scale

2.4.3 Elbow epicondylitis and platelet-rich plasma

The role of PRP injections in medial and lateral epicondylitis is at the very least questionable, with recent studies emerging with no better results than placebo. (Linnanmäki et al., 2020) Early studies by Peerbooms et al. (2010) and Gosens et al. (2011) had remarkable results greatly favouring PRP injections over CS in lateral epicondylitis. Gosens et al. (2011) reported ongoing positive effects lasting at least 2 years. The major issue with the studies was that CS are no longer recommended for use in lateral epicondylitis since PT and exercise treatments have better results in all but pain relief at 6 weeks of follow-up. (Karanasios et al., 2021) Thus far, CS treatments have been effective in the short-term follow-up of approximately 6 weeks; after that, the effect wears off, and symptoms tend to return with a risk of increased symptoms before CS injection. (Karanasios et al., 2021) Some studies suggest PRP is more efficient than CS regarding grip strength, elbow function, and pain after 1 month of follow-up and continue to be superior in the mid- to long-term follow-up. (Hohmann et al., 2023; Gupta et al., 2020) Table 7 summarises the most relevant clinical studies on chronic elbow epicondylitis.

Placebo-controlled studies have a history of presenting favourable results supporting PRP but recent studies indicate the effects of PRP injections for lateral epicondylitis are no greater than placebo; however, due to the accumulation of previous data meta-analyses continue supporting PRP use, albeit with caution. (Linnanmäki et al., 2020; Wong et al., 2022; Karjalainen et al., 2021) Niemiec et al.'s (2022) systematic review and meta-analysis evaluated the efficacy of PRP injections in light of minimal clinically important differences (MCID), concluding that PRP is seemingly an effective form of treatment for lateral epicondylitis. The type of PRP (LR-PRP or LP-PRP) used will unlikely matter regarding clinical outcomes for pain and functional improvement, although previous studies conflicted on that aspect, reporting lower complication rates of local pain after injection with LP-PRP than with LR-PRP but maybe marginally better PROMs with LR-PRP than with LP-PRP. (Shim et al., 2022; Li S et al., 2022) MCID values showed no distinction between the PRP types, with results being equally good. (Niemiec et al., 2022)

Occasionally literature depicts extracorporeal shock wave therapy (ESWT), botulinum toxin A, and dextrose prolotherapy (injecting sugar solution) as possible treatment options. (Liu W-C et al., 2022; Su et al., 2023) A meta-analysis suggests ESWT may be the best treatment for grip strength recovery, and ESWT and prolotherapy are the best treatments for pain relief in mid-term follow-up. (Liu et al, 2022) Botulinum toxin A, ESWT, and dextrose prolotherapy had better results than placebo in the short-term follow-up, but botulinum toxin A did not increase grip strength and only reduced pain better than placebo for up to 10 weeks. (Liu W-C et al., 2022; Su et al., 2023) However, due to the heterogeneity of the studies involved,

especially with ESWT, a great deal of caution should be taken in interpreting the results. (Liu W-C et al., 2022; Su et al., 2023) The literature search did not find studies directly comparing PRP to botulinum toxin A, so comparing these two treatments is based on various meta-analyses, suggesting botulinum toxin A may be better than PRP. (Liu W-C et al., 2022) It is worth considering that lateral epicondylitis may be a self-limiting condition, given that spontaneous resolution may occur within 24 months without any intervention, and chances of spontaneous resolution seem to be as high as 50% every 3 to 4 months. (Karjalainen & Buchbinder, 2023) This raises the question of, whether any treatment, except maybe exercise or PT, is beneficial in clinical practice. (Karanasios et al., 2021, Karjalainen & Buchbinder, 2023) Surgical interventions are not recommended for lateral epicondylitis, with a heavy emphasis on the self-limiting nature of the disease and valid conservative treatments. (Karjalainen & Buchbinder, 2023)

In summary, the overall heterogeneity of studies, lack of placebo-controlled studies comparing PRP and other treatment modalities, studies involving acute and chronic lateral epicondylitis, and lack of standardisation of the type of PRP used hinder the accurate interpretation of the current literature. (Wong et al., 2022; Niemiec et al., 2022) Despite this, the existing literature lean towards PRP not being any better than a placebo or any other treatment. (Linnanmäki et al., 2020; Wong et al., 2022; Liu W-C et al., 2022; Karjalainen & Buchbinder, 2023; Karjalainen T. et al., 2022) PRP is probably better than CS but given that CS should not be used in lateral epicondylitis, the result is completely irrelevant for clinical practice. (Karanasios et al., 2021; Karjalainen & Buchbinder, 2023) The type of PRP used will unlikely be of significance concerning results; however, only one study comparing LP-PRP and LR-PRP has been made in treating of lateral epicondylitis with no difference. (Shim et al., 2022; Li S et al., 2022; Niemiec et al., 2022; Yerlikaya et al., 2017) PRP is seemingly better than surgery but surgery is no longer recommended as a treatment for lateral epicondylitis so the basis of comparing which is a more effective treatment irrational. (Karjalainen & Buchbinder., 2023; Hardy et al., 2021) PT and exercise are probably superior treatments concerning efficacy and cost efficiency, but more extensive comparative studies of PRP are scarce. (Karanasios et al., 2021; Karjalainen T. el al., 2021) The literature does not support using PRP in lateral epicondylitis; the Finnish Current Care Guidelines also advocate against the use of PRP in the treatment of lateral epicondylitis. (Karjalainen T. et al., 2022, Overuse-related diseases of the hand and forearm: Current Care Guidelines, 2022)

Table 7. The most relevant original comparative studies of the clinical efficacy of PRP in elbow epicondylitis, based on study hierarchy

Original article	Patients	Study setting	Chronic or acute	Outcome and primary results	PRP effect (positive +, uncertain +/-, no effect -)
Linnanmäki, L. *et al.* (2020)	119 patients	RCT, double-blind, parallel-group study. Patients received LP-PRP or autologous blood or NS. Follow-up was 52 weeks.	Chronic lateral epicondylitis, with no response to initial nonoperative treatment	Primary outcome measure was VAS for pain. Secondary outcome measure was DASH. No clinically significant differences were found between the groups in VAS or DASH at any follow-up point.	-
Yerlikaya, M. *et al.* (2017)	90 patients	RCT, double-blind study. Patients received single injection LP-PRP or LR-PRP or an NS injection; all groups followed an exercise program. Follow-up was 8 weeks (at 4 and 8 weeks).	Chronic lateral epicondylitis and symptoms lasting over 3 months	Outcome measures were VAS for pain, PRTEE, grip dynamometer and pinchmeter, and extensor tendon thickness and cortical derangement. All outcome measures were nonsignificant between the groups at all follow-up points. All groups experienced a decrease in VAS and PRTEE, and improved grip and pinchmeter results compared to baseline at 4 and 8 weeks.	-
Mishra, A. K., *et al.* (2014)	230 patients	RCT, double-blind, prospective, multi-centre study. Patients received LR-PRP injections or dry needling. Follow-up was 24 weeks (4, 8, 12, and 24 weeks).	Chronic lateral epicondylitis with at least one failed conventional therapy and symptoms lasting at least 3 months.	Primary outcome measure was VAS for pain in resisted wrist extension. Secondary outcome measures were PRTEE and patient reports of tenderness in the elbow area. The PRP group had significantly better VAS at 8 and 24 weeks than the dry needling group. PRTEE showed no significant differences between the groups at any follow-up point. Patient reported tenderness at the elbow area was considerably lower in the PRP group at 24 weeks than in the dry needling group.	+/-
Martin, J. I., *et al.* (2019)	71 patients	RCT, double-blind, parallel-group study. Patients received an LP-PRP or lidocaine injection paired with percutaneous needle tenotomy. Follow-up was 12 months (6 weeks, 3 months, 6 months, and 12 months).	Chronic lateral or medial epicondylitis with previously failed conservative treatments and symptoms lasting at least 3 months.	Primary outcome measure was the percentage of patients who received a clinically relevant improvement in DASH. Secondary outcome measure was VAS for pain. There were no clinically significant differences between the groups regarding reaching MCID values for the outcome measures at 6 or 12 months.	-

Gosens, T., *et al.* (2011)	100 patients	RCT, double-blind study. Patients received a single injection of either LR-PRP or CS. Follow-up was 2 years (4, 8, 12, 26, 52, and 104 weeks).	Chronic lateral epicondylitis	Primary outcome measures were VAS for pain and DASH. PRP group had significantly greater improvement in VAS and DASH at 26 weeks and then, when compared to the CS group. The intent to treat the success rate was defined as a reduction of 25% of the VAS score; the PRP group had significantly more successfully treated patients than CS group.	+
Hastie, G., *et al.* (2018)	64 patients	Retrospective study. Chronic lateral epicondylitis patients had been offered surgery after they had failed conservative treatment, after which the policy was changed so that patients could try LR-PRP injection or opt for surgery. Follow-up was 7 years.	Chronic lateral epicondylitis	Outcomes were the yearly amount of epicondylitis surgeries and number of patients receiving benefits from the PRP injection, outcomes were compared before and after the change. The number of surgeries reduced significantly after the policy change; up to 87.5% of the PRP patients experienced reduced symptoms after PRP injection.	+/- (Retrospective study after policy change)
Watts, A. C., *et al.* (2020)	81 patients (final analysis 52 patients)	RCT. Patients were randomised to open surgery release or LR-PRP injection. Follow-up was 12 months (1,5, 3, 6, and 12 months).	Chronic lateral epicondylitis patients with a minimum of 6 months of symptoms, and had failed previous conservative treatments including CS injection	Primary outcome measure was PRTEE at 12 months. Secondary outcome measures were PRTEE at previous follow-up points. PRP and surgery produced similar functional outcomes, but patients who had surgery reported lower pain scores without significant differences to PRP. Up to 70% of the PRP patients had enough reduced symptoms to not consider surgery at 12 months.	+/-

Abbreviations: RCT: Randomized controlled trial; PRP: Platelet-rich plasma; LR-PRP: Leukocyte-rich platelet-rich plasma; LP-PRP: Leukocyte-poor platelet-rich plasma; NS: Normal saline; CS: Corticosteroid, VAS: Visual analogue scale; DASH: Disabilities of Arm, Shoulder and Hand; PRTEE: Patient related tennis elbow evaluation

2.5 Injection technique

The injection technique for intraarticular injections of PRP in the knee is simple; the technique is the same as for all intraarticular knee injections. The goal is to inject the PRP solution into the knee joint for the PRP to have any useful effect on the joint pathology. Injections are performed with careful antiseptic swiping of the skin area, maintaining an aseptic environment throughout the procedure. Anatomical landmarks are identified before the needle is inserted through the skin. (Luosujärvi, 2020) Various techniques have been described in the literature ranging from ultrasonography (US) guided to anatomical landmark-guided techniques. (Chernchujit et al., 2019; Rijs et al., 2021) The most common landmark-guided techniques are the standard superolateral and modified anterolateral approaches, with or without combining joint effusion aspiration or air injection to the knee to confirm the needle position. (Chernchujit et al., 2019; Luosujärvi, 2020) Landmarks that guide the clinician are the upper part of the patella, the lateral epicondyle of the femur, the patellar joint, and the adjacent soft spot and bony edges of the tibia. (Chernchujit et al., 2019; Luosujärvi, 2020) In Finland the technique is largely up to the medical professional to decide; currently, general practitioners' guides advise to using anatomical landmarks guided injections with the standard superolateral approach, but for example, for morbidly obese patients the modified anterolateral approach may be easier to perform. (Luosujärvi, 2020) US guidance is not routinely used, as the injection accuracy is 89% to 96% with appropriate confirmations made during the injection; however, the lack of experience in performing the injection and choosing a suboptimal technique may increase the chance of missing the joint space. (Chernchujit et al., 2019; Fang et al., 2021) If the joint has a significant amount of effusion, the excess is removed via aspiration before injecting solution into the joint. (Luosujärvi, 2020) Table 8 lists the summary for injection accuracies and landmarks.

The injection technique for the shoulder in Finland is also up to the medical professional to decide; the National General Practitioners' Guide recommends two landmark-guided options; the anterior and posterior approaches for injections. (Luosujärvi, 2020) Landmarks used in the posterior approach are the ridge of the scapula, the glenohumeral joint crevice, and the head of the humerus. (Luosujärvi, 2020) The needle is inserted in a straight line towards the palpable joint crevice. (Luosujärvi, 2020) A posterior approach is safer than the anterior approach because there are no large nerves or vessels in the direct area of the needle course. (Luosujärvi, 2020) Landmarks for the anterior approach are the distal end of the clavicle, the glenohumeral joint crevice when the arm is slightly abducted and rotated outward, and the upper area of the head of the humerus. (Luosujärvi, 2020) In the anterior approach, the needle is guided towards the joint crevice at a 30-degree angle. (Luosujärvi, 2020) There is evidence that the landmark-guided anterior approach

would be more accurate than the landmark-guided posterior approach with accuracy ranging from 78% in the posterior approach to 94% in the anterior approach. (Rijs et al., 2021) US is not routinely recommended in Finland, although studies show it is more accurate in shoulder area injections in general; however, it does not significantly improve subacromial injections, especially since the landmark guided anterior approach offers nearly the same accuracy. (Aly et al., 2015, Ali et al., 2021) Table 8 lists a summary of injection accuracies and land-marks.

The injection technique for lateral epicondylitis is likewise performed under aseptic conditions; in Finland, the technique is up to the medical professional to decide. However, landmark-guided techniques are more common in general practice. The injection site is found via palpation, and the injection is guided towards the most tender point of the lateral epicondyle of the humerus, where the common extensor of the forearm is located. (Gulabi et al., 2017) The so-called “peppering technique”, which means injecting small amounts of the solution to several adjacent spots in the most tender side of the lateral epicondyle through a single-entry point in the skin to ensure a thorough spread of the solution, is probably not any better than injecting all the solution into a single point. (Gulabi et al., 2017) Little data exists on the accuracy of landmark-guided injections for elbow epicondyles, but US-guided injections are significantly more accurate than landmark-guided injections. (Keijsers et al., 2017) The closest estimates for accuracy would be from elbow joint injections, where US-guided accuracy is ranging from 91% to 100% and land-mark-guided accuracy ranges from 64% to 100%. (Patel R., et al., 2023) A careful antiseptic technique is advised for all injections. (Luosujärvi, 2020) Table 8 lists a summary of injection accuracies and land-marks.

Table 8. Anatomical land-marks and accuracy of different injection techniques with and without ultrasonography.

Injection technique	Accuracy with ultrasonography	Accuracy without ultrasonography	Anatomical land-marks
Knee supero-lateral approach	95–100% (Fang et al., 2021; Chernchujit et al., 2019; Rijs et al., 2021)	58–95% (Fang et al., 2021; Chernchujit et al., 2019; Rijs et al., 2021)	Upper edge of patella, lateral epicondyle of the femur, patellofemoral joint crevice
Knee antero-Lateral approach	98.5% (Fang et al., 2021; Chernchujit et al., 2019; Rijs et al., 2021)	86–96% (Fang et al., 2021; Chernchujit et al., 2019; Rijs et al., 2021)	Lateral / distal edge of patella, patellar tendon, proximal edge of tibia, soft spot of the tibiofemoral joint crevice
Gleno-humeral joint posterior approach	92.5%	72.5–78% (Rijs et al., 2021)	Ridge of scapula, glenohumeral joint crevice (soft spot), the head of the humerus
Gleno-humeral joint anterior approach	96–100% (Ali et al., 2021)	94% (Rijs et al., 2021)	Distal end of the clavicula, glenohumeral joint crevice, the head of the humerus
Shoulder subacromial space	65% (Aly et al., 2015)	70% (Aly et al., 2015)	Lateral edge of the acromion and the soft spot right under it
Elbow epicondyles	No data available; US-guided accuracy to elbow joint according to literature is 91–100% vs non-US-guided accuracy 64–100% (Patel R et al., 2023)	30–60% (Keijsers et al., 2017)	Palpable epicondyles in the distal humerus (medially and laterally). Injection is usually made to most tender spot or near it.

3 Aims

1. To evaluate intra-articular autologous PRP injections clinical efficacy and postpone the need for arthroplasty in KOA when compared to hyaluronic acid injections.
2. To study which is more effective: subacromial CS injections or autologous PRP injections in treating RC tendinopathy.
3. To investigate if autologous platelet-rich plasma injections are effective in chronic lateral epicondylitis when other conservative treatment options are exhausted.
4. To determine if intra-articular autologous PRP injections have different efficacy in different stages of KOA.
5. To study if intra-articular autologous platelet-rich plasma injections have different efficacy in obese or non-obese patients with KOA.

4 Materials and Methods

Patients in Studies I to V were treated in the District Hospital of Forssa, Welfare District of Forssa, Finland, between 2014 and 2020. Data for all the studies was collected retrospectively from the electronic patient archives. Studies I to V were conducted in accordance with the Declaration of Helsinki ethical principles. The Institutional Review Board approved the studies. Individual informed consent was waived due to the studies' retrospective nature and source data's de-identification. Table 9 includes an overview of the patients and methods for each study.

Table 9. Overview of the patients and methods of Studies I to V.

Study	Patients, years, follow-up	Disease and study setting	Inclusion and exclusion criteria	Outcome measures
Study I	2014 to 2017 Total patients n = 180 PRP n = 94 (mean age 57.4 ± 10.3, females 63.8%, mean K-L grade 2.3 ± 0.6) HA n = 86 (mean age 65.7 ± 9.2, females 58.1%, mean K-L grade 2.4 ± 0.6) Mean follow-up at least 16 months.	Mild to moderate KOA (K-L 1 to 3). Patients received 3 intra-articular injections of LR-PRP at a 10 to 14 days interval or 1 to 3 injections of HA. This study sought to find, whether PRP postpones the need for arthroplasty and which treatment is better for treating KOA symptoms.	Inclusion criteria: KOA of K-L 1 to 3 diagnosed with radiographic imaging, age 18–90, pretreatment VAS for pain between 30–100. Exclusion criteria: patients with major systemic disorders (haematological diseases, ongoing infection, immunodeficiency, active or fulminant rheumatoid disease etc), major symptomatic HOA of the same side, pregnancy, or possible pregnancy.	WOMAC VAS for pain ROM arthroplasty
Study II	2014 to 2018 Total patients n = 75 CS n = 40 (mean age 55.3 ± 12.3, females 57.5%) PRP n = 35 (mean age 53.5 ± 12.8, females 80.0%) Mean follow-up at least 21 months.	Symptomatic RC tendinopathy patients, with or without minor RC tear, received 3 injections of LR-PRP at a 10 to 14 days interval or a single injection of CS. CS injection was given subacromially; PRP injection was given subacromially or around the tendon or lesion. This study compared PRP injections to CS injections in degenerative RC tendinopathy.	Inclusion criteria: RC tendinopathy, other causes for shoulder pain ruled out by imaging and clinical examination, age 18–90, preintervention VAS for pain 30–100. Exclusion criteria: fractures, nerve-related symptoms, frozen shoulder, traumatic RC ruptures, full thickness RC ruptures, long tendon of the biceps muscle tears, labrum tears, OA of the glenoid-humeral joint, OA of the acromion-clavicular joint, general conditions requiring surgical intervention as primary care and patients with major systemic disorders (haematological diseases, infections, immunodeficiency), pregnancy, possible pregnancy and patients who used other oral medication than NSAID or APAP or any kind of injection other than PRP or CS.	WORC VAS for pain ROM Surgical intervention
Study III	2014 to 2020 Total patients n = 55 PRP n = 25 (mean age 53.6 ± 8.4, females 44.0%)	Chronic elbow epicondylitis with symptoms over 6 months and previously failed conservative treatments. Patients received single injections of LR-PRP and	Inclusion criteria: chronic lateral epicondylitis with symptoms for over 6 months, age 18–90, preintervention VAS for pain 30–100, no previous response to conservative treatment.	Surgical intervention VAS for pain DASH PRTEE

	PT n = 30 (mean age 48.4 ± 9.9, females 76.6%) Mean follow-up at least 36 months	continued PT exercises or only continued PT exercises. Study sought to find if PRP injection intervention would help patients with chronic elbow epicondylitis better than conventional treatment.	Exclusion criteria: other confounding diseases or conditions affecting the upper extremity such as carpal tunnel syndrome, ulnar nerve entrapment, neurological diseases, cervical spine radiculopathy, cervical spine disorders, recent trauma of the upper extremity, fractures, elbow joint OA, other injection therapies of the elbow area more than 6 months prior, major systemic disorders (haematological diseases, infections, immunodeficiency), previous elbow area surgery (e.g. surgery due to epicondylitis or trauma), patients without chronic epicondylitis.	
Study IV	Years 2014 to 2017 Total patients n = 91 K-L 1 n = 9 (mean age 59.9±10.0, females 66.7%) K-L 2 n = 49 (mean age 56.6±10.4, females 61.2%) K-L 3 n = 33 (mean age 58.1±10.4, females 60.6%) Mean follow-up was at least 14 months	Mild to moderate K-L 1 to 3 KOA. Patients were divided into 3 study arms according to K-L classification and received 3intra-articular injections of LR-PRP. The study sought to find if the degree of KOA affects PRP's clinical efficacy.	Inclusion criteria: K-L grade 1 to 3 KOA, age 18–90, pre-intervention VAS 30–100. Exclusion criteria: age 18–90, major systemic disease (e.g. haematological diseases, infections, immunodeficiency, active or fulminant rheumatoid disease), K-L 4 graded KOA, pregnancy, possibility of pregnancy.	WOMAC VAS for pain ROM
Study V	2014 to 2017 Total patients n = 91 BMI > 30 kg/m^2 n = 34 (mean age 56.1±9.8, females 67.6%, mean BMI 33.6±3.9) BMI < 30 kg/m^2 n = 57 (mean age 58.3±10.6, females 57.9%, mean BMI 26.0±1.9) Mean follow-up at least 13 months	Mild to moderate K-L 1 to 3 KOA. Patients were divided into two study arms (BMI < 30 kg/m^2 or > 30 kg/m^2) and received 3 intra-articular injections of LR-PRP. This study sought to find if obesity affects PRP's clinical efficacy in mild to moderate KOA.	Inclusion criteria: age 18–90, KOA K-L 1 to 3, VAS between 30 to 100. Exclusion criteria: major systemic diseases (e.g. haematological diseases, active or fulminant rheumatoid disease, immunodeficiency, infection), younger than 18 or older than 90, clinically relevant HOA of the same side, pregnancy, possibility of pregnancy.	WOMAC VAS for pain ROM

Abbreviations: PRP: Platelet-rich plasma; HA: Hyaluronic acid; KOA: Knee osteoarthritis; LR-PRP: Leukocyte-rich platelet-rich plasma; K-L: Kellgren-Lawrence grading; VAS: Visual Analogue Scale; HOA: Hip osteoarthritis; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; ROM: Range of motion; CS: Corticosteroid; RC: Rotator cuff; WORC: Western Ontario Rotator Cuff Index; OA: Osteoarthritis; NSAID: Non-steroid anti-inflammatory drug; APAP: Acetaminophen; DASH: Disabilities of Arm, Shoulder and Hand; PRTEE: Patient related tennis elbow evaluation; BMI: Body mass index

4.1 Platelet-rich plasma preparation and injections

The PRP used in Studies I to V was manufactured with a commercial GLO PRP kit (GloFinn corporation, Salo, Finland). The manufacturing of PRP, according to the kit instructions began with a trained nurse drawing 10 mL of venous blood, followed by centrifugation of the blood for 5 minutes at 1200 rounds per minute. Excess red blood cells were removed and a second centrifugation of 10 minutes was completed, resulting in a final product of PRP with a 4- to 8-times higher concentration of platelets than whole blood. The final product was LR-PRP since leukocytes were not discarded. Figure 1 presents the kit instructions in detail.

An experienced orthopaedist performed the injections using anatomical landmarks as guidance for intra-articular knee injection, shoulder injection, and injection to the lateral epicondyle area of the elbow, where respective extensor muscle insertions lay. The amount of PRP injected in Studies I, IV, and V was approximately 4–5 mL per injection time, with three injections performed at a 10- to 14-days interval. The amount of PRP injected in Studies II and III was approximately 1–2 mL, and the injection in Study II was aimed at the subacromial space or around the tendon lesion site. The amount of PRP was smaller in studies II and III due to the anatomical location and the reasonable amount that could be injected into the site.

1. Verinäyte

(1) Lisää GLO PRP ruiskuun 1,0 ml antikoagulanttia (**Natrium Citricum** hyytymisen estoaine).

(2) Ota siipineulalla verta 9,0 ml suoraan GLO PRP ruiskuun.

(3) Lisää GLO PRP -ruiskuun punasolunkerääjä-osa (RBC- osa).

(4) GLO PRP ruiskun varsi irtoaa kääntämällä sitä vastapäivään ja painamalla hieman samaan aikaan varren tiivisteosasta.

(5) Käänteile GLO PRP ruiskua muutaman kerran jotta natriumsitraatti ja veri sekoittuvat.

2. Ensimmäinen sentrifugointi

(6) Paina "PROGRAM" -painiketta, valitse 1.

(7) Paina uudelleen "PROGRAM" -painiketta, näytölle tulee lukema 5 *(5 minuuttia)*.

Huomioi että sentrifugissa tulee aina pysyä tasapaino! Jos käsittelet 1 tai 3 ruiskua, lisää sentrifugiin vastapainoksi laitteen mukana toimitettu **vaaleanpunainen** ruiskupaino.

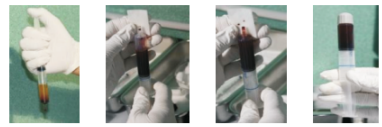
(8) Laita GLO PRP ruisku sentrifugiin,sulje kansi ja paina "SOFT START" -painiketta käynnistääksesi sentrifugin.

3. Punasolujen eroittaminen

HUOM! Pidä kohtien 9-11 aikana GLO PRP - ruiskua koko ajan pystysuorassa, jottei veren eri kerrokset sekoittuisi.

(9) Laita varovasti GLO PRP ruiskun varsi paikalleen kääntämällä sitä myötäpäivään.

(10) Irrota varovasti punasolunkerääjä (RBC-osa) GLO PRP ruiskusta .



(11) Paina varovasti GLO PRP ruiskusta jäljelle jääneet punasolut pois siihen asti kunnes punasolujen selkeä pinta saavuttaa 0ml sinisen rajaviivan.

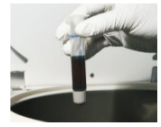
(12) Käännä GLO PRP ruisku ylösalaisin ja paina ruiskusta ylimääräinen ilma pois.

(13) Laita GLO PRP ruiskuun harmaa korkki.

(14) Kierrä PRP ruiskun varsi irti kääntämällä sitä vastapäivään ja painamalla hieman samaan aikaan varren tiivisteosasta.

4. Toinen sentrifugointi

Jos käsittelet 1 tai 3 ruiskua, lisää sentrifugiin vastapainoksi laitteen mukana toimitettu **keltainen** ruiskupaino.



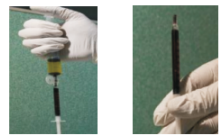
(15) Paina "PROGRAM" -painiketta, valitse 2 ja paina uudelleen "PROGRAM" -painiketta, näytölle tulee lukema 10 (*10 minuuttia*). Käynnistä "SOFT START" -painikkeesta

5. PRP (Platelet Rich Plasma)

HUOM! Pidä kohtien 17-20 aikana GLO PRP - ruiskua koko ajan pystysuorassa, jottei veren eri kerrokset sekoittuisi.

(16) Laita varovasti GLO PRP ruiskun varsi paikalleen kääntämällä sitä myötäpäivään ja irroita harmaa korkki.

(17) Laita GLO PRP ruiskuun pakkauksen mukana tullut liitin ja kiinnitä 1ml ruisku liittimeen.



(18) Paina GLO PRP ruiskusta, jotta 1ml ruisku täyttyisi.

(19) Rikastettu plasma on nyt valmis ruiskutettavaksi 1 ml ruiskusta.

Jos GLO PRP -laitetta on käytetty muuhun toimenpiteeseen ja valmiiksi asetettu ohjelma on kadonnut, tee seuraavasti kohdassa

(6) Paina "RPM/RCF" - painiketta, niin että valo on kohdassa **RCF**. Valitse kierrosnopeudeksi **1200**.

(7) Paina "TIME" - painiketta ja valitse ajaksi **5 minuuttia**.

(15) Laita GLO PRP ruisku sentrifugiin ja aseta kierroksiksi (RCF) **1200**, ajaksi (TIME) **10 min**, ja käynnistä sentrifugi SOFT START-painikkeesta.

Figure 1. GloPRP kit instructions for PRP preparation in Forssa District Hospital, Forssa, Finland. Photograph of the instructions taken by Aleksi Annaniemi.

4.2 Study I Patients and methods

Study I patients included all patients who had received intra-articular injections of autologous PRP or HA between January 2014 and October 2017 for KOA in the District Hospital of Forssa, Welfare District of Forssa, Finland. Data was collected retrospectively from the electronic patient archives. Demographic data was collected, and inclusion and exclusion criteria were applied. Inclusion criteria were KOA of Kellgren-Lawrence (K-L) 1–3 diagnosed with radiographic imaging, age 18–90, and pretreatment Visual Analogue Scale (VAS) for pain between 30–100. Exclusion criteria were: patients with major systemic disorders (haematological diseases, ongoing infection, immunodeficiency, active or fulminant rheumatoid disease etc), major symptomatic HOA of the same side, pregnancy, or possible pregnancy. Altogether, 180 consecutive patients were included in the study I, 94 patients in the PRP group and 86 in the HA group.

An evaluation of the KOA symptoms was conducted with Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and VAS for pain and range of motion (ROM) of the knee. The primary outcome measure for the Study I was the occurrence of any knee arthroplasty after intra-articular injections. Secondary outcome measures were VAS, WOMAC, ROM, and the occurrence of adverse events. Study I's follow-up points were before the intervention, 15 days after the intervention, 6 months, 12 months, and the last follow-up.

Altogether, 79 patients in the HA group had received one injection of high molecular weight HA (Hylan G-F 20, Synvisc One®, Naarden, Netherlands, 6,000,000 Da, 48 mg / 6 ml injection or Sodium Hyaluronate, Arthrum75®, Chartres, France, ≥2,800,000 Da, 75 mg / 3 ml injection) and 5 patients received low molecular weight HA (Hyalgan®, Abano Terme, Italy, 500,000–730,000 Da, 20 mg / 2 ml injection). Patients in the PRP group had received three injections of autologous PRP (commercial GLO PRP kit, GloFinn Corporation, Salo, Finland) at a 10- to 14-days intervals. Three patients received fewer than three injections and five patients received more than one treatment, meaning more than three injections.

4.2.1 Statistical analysis of Study I

Mean ± standard deviation was used to report continuous variables. Normality assumptions were established by analysing histograms, assessing kurtosis and skewness, and employing Kolmogorov/Smirnov tests for primary endpoints. Appropriate Pearson's chi-square test, Fisher's exact test, and the Mann-Whitney test or t-test were used for univariate analysis. The likelihood of a patient being included in the PRP or HA group was analysed with logistic regression with backward selection. A regression model fit was analysed with Hosmer-Lemeshow's test. The propensity score was calculated and used for one-to-one matching;

moreover, the score was utilized to assess other variables in estimating their impact on postoperative outcomes. The nearest neighbour method and calliper of 0.2 of the standard deviation of the logit of the propensity score were chosen for one-to-one propensity score matching between the PRP and HA groups. Continuous outcomes were compared in propensity score-matched groups using paired t-test or the Wilcoxon signed rank-test as appropriate. Differences in proportions were compared using McNemar's or binomial test as appropriate.

Kaplan-Meier's method was used to evaluate the survival function of TKA in the propensity score matched pairs and the overall series of patients. Kaplan-Meier's methods were used to assess the long-term outcomes in the overall series and the propensity-matched pairs with the log-rank test and the Cox proportional hazards method with a log minus log test. P-values < 0.05 were considered statistically significant. All analyses were carried out using SPSS statistical software (IBM SPSS Statistics, version 23, Armonk, NY).

4.3 Study II patients and methods

Patients included in Study II were consecutive patients with RC disorders from the District Hospital of Forssa, Welfare District of Forssa, Forssa, Finland, between January 2014 and December 2018. The data was collected retrospectively from the electronic patient archives. Altogether, 98 patients were analysed and inclusion and exclusion criteria were applied. Patients received CS injection or PRP injections for their RC disease. The final study protocol consisted of 75 patients after inclusion and exclusion criteria were applied. The CS group had 40 patients; the PRP group had 35.

Inclusion criteria were: diagnosed RC tendinopathy; other causes for shoulder pain were ruled out by imaging and clinical examination, age 18–90, preintervention VAS for pain 30–100. MRI, radiographs, and US were used as imaging modalities to rule out other disorders unfit to be RC tendinopathy, as well as clinical examination by an experienced orthopaedist. Patients with small partial RC tears or intra-tendinous tears with degenerative origin were included in Study II. Typical findings in the MRI were tendinosis/tendinopathy/tendinitis of the supraspinatus muscle tendon with or without subacromial bursitis. Sometimes these findings were accompanied by tendinosis/tendinopathy/tendinitis of other RC muscle tendons (infraspinatus, teres minor, or subscapularis). One patient of the CS group did not have supraspinatus tendinosis/tendinopathy/tendinitis but only infraspinatus tendinosis/tendinopathy/tendinitis. The PRP group had one patient with a minor intra-tendinous rupture of the supraspinatus tendon with tendinosis included.

The exclusion criteria were: fractures, nerve-related symptoms, frozen shoulder, traumatic RC ruptures, full thickness RC ruptures, long tendon of the biceps muscle

tears, labrum tears, OA of the glenoid-humeral joint, OA of the acromion-clavicular joint, general conditions requiring surgical intervention as primary care and patients with major systemic disorders (haematological diseases, infections, immunodeficiency), pregnancy, possible pregnancy and patients who used oral medication other than NSAID or acetaminophen (APAP) or received any other kind of subacromial injection other than PRP or CS.

The CS group received one injection of methylprednisolone acetate 2 mL (40 mg/mL) (Solomet, Orion Oyj, Espoo, Finland, or Depo-Medrol Pfizer Inc, New York City, New York, United States) subacromially. The PRP group received three 1–2 mL injections of autologous PRP (commercial GLO PRP kit, GloFinn Corporation, Salo, Finland) at a 10- to 14-day interval. Both groups were instructed with routine PT instructions to rehabilitate the shoulder as part of routine care. The primary outcome measure for Study II was the Western Ontario Rotator Cuff Index (WORC). The secondary outcome measures were VAS for pain, ROM, and the patient ending up in surgical intervention. The follow-up points were before the intervention, 6 months, 12 months, 18 months, and the last follow-up.

4.3.1 Statistical analysis of Study II

Parametric and nonparametric measures were reported as mean ± standard deviation. Normality assumptions were determined using histograms, kurtosis, skewness, and Kolmogorov/Smirnov tests. Post hoc statistical power for the primary outcome measure was 47.5% including an observed effect size of 0.436 (Cohen's d). The Student's t-test was used for continuous variables, and the Fisher's exact test was used for discrete variables, to compare the two study groups, according to the data type. All analyses were conducted using SPSS statistical software (IBM SPSS Statistics, version 23, Armonk, NY).

4.4 Study III patients and methods

Patients included in Study III were treated for chronic lateral epicondylitis in the District Hospital of Forssa, Welfare District of Forssa, Forssa, Finland, between 2014 and 2020. This was a retrospective study and the data was collected from the electronic patient records for analysis. Altogether, 55 consecutive patients were included in Study III. The patients previously failed PT as a conservative treatment and were qualified having a chronic state of the disease with symptoms having persisted over 6 months.

The inclusion criteria for Study III were the following: diagnosis of chronic lateral epicondylitis with symptoms for over 6 months, age 18–90, preintervention VAS for pain between 30–100, and no previous response to conservative treatment.

The exclusion criteria were: other confounding diseases or conditions affecting the upper extremity such as carpal tunnel syndrome, ulnar nerve entrapment, neurological diseases, cervical spine radiculopathy, cervical spine disorders, recent trauma of the upper extremity, fractures, elbow joint OA, previous other injection therapies of the elbow area before 6 months, major systemic disorders (haematological diseases, infections, immunodeficiency), previous elbow area surgery (e.g. surgery due to epicondylitis or trauma) and patients without chronic epicondylitis. To simplify, the patients enrolled in Study III had chronic lateral epicondylitis and had not received help from conventional gold-standard PT.

The enrolled patients then continued physical therapy or received a one injection of 2 mL autologous PRP (commercial GLO PRP kit, GloFinn Corporation, Salo, Finland). Patients were prescribed ibuprofen 600 mg three times a day and/or acetaminophen (APAP) 1g a maximum of three times a day as pain medication, taken when needed. An experienced physical therapist instructed the patients with the exercises, which patients were instructed to do at least three times a day. PT consisted of wrist curls, finger stretching, wrist and finger extensor and flexor stretching, wrist rotations, and gripping or squeezing a softball; the exercises were performed with or without weight up to half a kilogram, depending on one's level of strength.

Data were collected before the intervention, at 6 months, 12 months, 24 months, 36 months, and at the last follow-up. The primary outcome measure was the patient having surgery for elbow epicondylitis during the follow-up. The secondary outcome measures were VAS for pain, Disabilities of the Arm, Shoulder, and Hand (DASH), and Patient-Related Tennis Elbow Evaluation (PRTEE).

4.4.1 Statistical analysis of Study III

Continuous parametric and nonparametric data were reported as mean ± standard deviation. Percentages were used for discrete data. Histograms, kurtosis, skewness, and, for primary endpoint, Kolmogorov/Smirnov tests were utilised to establish normality assumptions. A two-sided P value ≤ 0.05 on a 95% confidence interval (CI) was considered statistically significant. The Student's t-test for continuous variables and Fisher's exact test for discrete variables were used for intergroup comparison. All analyses were carried out using SPSS statistical software (IBM SPSS Statistics, version 23, Armonk, NY).

4.5 Study IV patients and methods

Study IV was a retrospective study with 91 patients with symptomatic KOA, who were treated with three autologous intra-articular PRP injections at the Welfare

District of Forssa, Finland, between January 2014 and October 2017. Patient data was collected from electronic medical records for the analysis. PRP injections were given at a 10- to 14-day interval. The inclusion criteria for Study IV were Kellgren-Lawrence (K-L) grade 1 to 3 KOA in radiographic imaging, age 18–90, and pre-intervention VAS between 30–100. The exclusion criteria were age younger than 18 or older than 90, major systemic disease (e.g. haematological diseases, infections, immunodeficiency, active or fulminant rheumatoid disease), K-L 4 graded KOA, pregnancy, or the possibility of pregnancy.

The primary outcome parameter was WOMAC; the secondary outcome parameters were VAS and ROM. The follow-up points were 15 days after the first injection, 6 months, 12 months, and/or the last follow-up. Adverse events were documented. Demographic data were collected from the electronic medical records. Patients were divided into three groups based on the K-L grading of their KOA. Group A had K-L grade 1 KOA, Group B had K-L grade 2 KOA and Group C had K-L grade 3 KOA. The PRP injections were autologous and prepared with a commercial kit by GloFinn (commercial GLO PRP kit, GloFinn Corporation, Salo, Finland) according to the manufacturer's instructions.

4.5.1 Statistical analysis of Study IV

Continuous variables were reported as the mean ± standard deviation. Normality assumptions were demonstrated with histograms, skewness, kurtosis, and Kolmogorov/Smirnov tests. Pearson's chi-square test, Fisher's exact test, and the Mann-Whitney U test or *t-test* were used for univariate analysis, as appropriate, for comparisons between the study groups according to the Kellgren-Lawrence grading. A two-sided *p-value* less than 0.05 was considered statistically significant. All analyses were carried out using SPSS statistical software (IBM SPSS Statistics, version 23, Armonk, NY).

4.6 Study V patients and methods

Altogether, 91 patients with symptomatic KOA were included in this retrospective study to determine if BMI is a factor regarding PRP efficacy. Patients had mild to moderate KOA with K-L 1 to 3 grading. All patients received three injections of autologous intra-articular PRP between January 2014 and October 2017 at the Welfare District of Forssa, Finland. Data were collected from electronic medical records and included demographic data.

Inclusion criteria for Study V were age 18–90, mild to moderate KOA (K-L grade 1 to 3) in radiographs, and VAS 30–100. Exclusion criteria were major systemic diseases (e.g. haematological diseases, active or fulminant rheumatoid

disease, immunodeficiency, infection), age younger than 18 or older than 90, clinically relevant hip osteoarthritis of the same side, pregnancy, or the possibility of pregnancy. The primary outcome parameter was WOMAC; the secondary outcome parameters were VAS and ROM. Outcome measures were analysed before the intervention, at 15 days, 6 months, 12 months, and/or at the last follow-up after injections. Patients were divided into two groups based on their body mass index (BMI). Group A included obese patients, with a BMI over 30 kg/m2 and Group B included non-obese patients, with BMI less than 30 kg/m2.

The PRP injections were autologous and prepared with a commercial kit by GloFinn (commercial GLO PRP kit, GloFinn corporation, Salo, Finland) according to the manufacturer's instructions. Each patient received three intra-articular injections of PRP, at a 10- to 14-day interval.

4.6.1 Statistical analysis of Study V

A statistical analysis was conducted using SPSS statistical software (IBM SPSS Statistics, version 28, Armonk, NY). Continuous variables were described as mean ± standard deviation. Normality assumptions were established by histograms, kurtosis, skewness, and with Kolmogorov/Smirnov tests. Pearson's chi-square test, Fisher's exact test, and t-test were employed for carrying univariate analysis, as appropriate, for comparisons between the two study groups according to the BMI (obese, >30 kg/m^2 vs non-obese, <30 kg/m^2). A two-sided p-value less than 0.05 was considered statistically significant. The post hoc statistical power was calculated as 47.5% for the primary outcome measure, considering an observed effect size of 0.436 (Cohen's d).

5 Results

Studies I to V showed mostly positive results for PRP versus HA in KOA and PRP versus PT in elbow epicondylitis; patients with milder KOA and lesser BMI benefitted more from PRP treatments than patients with more advanced KOA or higher BMI. PRP was on equal terms versus CS injections in RC tendinopathy. Only a few mild adverse events but no serious adverse events were found. All the adverse events were similar to other injection treatments. Patients with mild to moderate KOA had their arthroplasty postponed further with intra-articular PRP injections rather than with intra-articular HA injections. Chronic elbow epicondylitis patients had a remarkable recovery and improvement in PROMs, which the PT group took over 24 months to achieve.

5.1 Platelet-rich plasma in mild to moderate knee osteoarthritis (Studies I, IV, and V)

Studies I, IV, and V included patients with mild to moderate KOA. Table 10 lists the key findings of Study I. In Study I, the overall series PRP group had significantly better WOMAC overall scores than the HA group at 15 days, 6 months, 12 months, and at the last follow-up point. Similarly, VAS for pain scores were lower in the PRP group than in the HA group at 15 days, 6 months, 12 months, and at the last follow-up. (Table 10) Likewise, the analysis of propensity score-matched pairs showed that the PRP group had lower VAS at 6 months, 12 months, and at the last follow-up and better WOMAC scores at 6 months and the last-follow-up, than the HA group. (Table 10) Both analyses showed the PRP group had significantly fewer arthroplasties than the HA group. (Table 10)

The key results of Study IV were that Group A with the mildest KOA had significantly better VAS for pain at 6 months and the last follow-up than Group C, with the most advanced KOA. The WOMAC overall score was also significantly lower in Group A than in Group C at the last follow-up. (Table 11)

The only significant result of Study V was that Group B with lower BMI had a better WOMAC overall score at the last follow-up than Group A with higher BMI (Group A 17.8 ± 18.8 vs Group B 10.5 ± 11.7, $p = 0.023$). In turn, the intra-articular PRP injections seemingly provided similar results regardless of BMI, as all the other PROMs were non-significant between the two groups (all $p > 0.05$) during the follow-up.

Table 10. Most relevant results of Study I, including overall series and propensity score-matched pairs. Values expressed in mean range for PROMs.

	Overall Series			**Propensity Score-Matched Pairs**		
	PRP group	**HA group**	*p*-value	**PRP group**	**HA group**	*p*-value
	N = 94	**N = 86**		**N = 39**	**N = 39**	
WOMAC overall (15 days)	20.1 (0–66)	25.3 (0–66)	0.021	21.2 (0–52)	22.6 (0–52)	0.658
VAS (0-100) (6 months)	18.9 (0–100)	45.5 (0–100)	<0.001	26.3 (0–90)	45.0 (0–90)	0.007
WOMAC overall (6 months)	10.7 (0–69)	27.3 (0–66)	<0.001	15.7 (0–66)	24.7 (0–66)	0.016
VAS (0-100) (12 months)	21.1 (0–99)	47.1 (0–100)	<0.001	27.6 (0–95)	42.7 (0–99)	0.043
VAS (0-100) (last follow-up)	21.4 (0–99)	52.7 (0–99)	<0.001	29.5 (0–99)	54.5 (0–99)	<0.001
WOMAC overall (last follow-up)	12.8 (0–81)	32.0 (0–99)	<0.001	19.2 (0–76)	30.2 (0–81)	0.012
Any knee arthroplasty	5 (5.3%)	31 (36.0%)	<0.001	5 (12.8%)	16 (41.0%)	0.010
UKA	2 (2.1%)	18 (20.9%)	<0.001	2 (5.1%)	9 (23.1%)	0.047
TKA	3 (3.2%)	13 (15.1%)	0.007	3 (3.8%)	7 (17.9%)	0.310

Abbreviations PROM: Patient reported outcome measure; BMI: Body mass index; VAS: Visual Analogue Scale for pain; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; PRP: Platelet-rich plasma; HA: Hyaluronic acid; UKA: Unicondylar knee arthroplasty; TKA: Total knee arthroplasty

Table 11. Most relevant results of Study IV as intergroup comparisons and their *p*-values between Groups A, B and C during the follow-up. [a]Group A vs group B, [b] Group B vs group C, [c] Group A vs group C. Values expressed in the mean range for PROMs.

	Group A (K-L 1)	**Group B (K-L 2)**	**Group C (K-L 3)**	***p-value*[a]**	***p-value*[b]**	***p-value*[c]**
	n = 9	n = 49	n = 33			
VAS (0-100) (6 months)	5.6 (0–30)	20.4 (0–90)	21.6 (0–70)	0.096	0.840	0.031
VAS (0-100) (last follow-up)	8.9 (0–50)	22.3 (0–85)	25.3 (0–90)	0.135	0.608	0.029
WOMAC overall (last follow-up)	5.1 (0–24)	12.7 (0–53)	16.2 (0–71)	0.113	0.311	0.008

Abbreviations PROM: Patient reported outcome measure; VAS: Visual Analogue Scale for pain; WOMAC: Western Ontarion and McMaster Universities Osteoarthritis Index; K-L: Kellgren-Lawrence classification

5.1.1 Platelet-rich plasma versus hyaluronic acid (Study I)

The two groups had statistically significant differences in their baseline demographics of age, prevalence of obesity, comorbidity, diabetes and overall WOMAC score, which all were statistically significantly higher in the HA group than the PRP group (all $p < 0.05$). The mean follow-up in both groups was over 17 months. The overall series of patients included 94 patients in the PRP group and 86 in the HA group. The propensity score analysis included 39 patients from both groups who were matched pairs to reduce the baseline differences between the two groups. Per study protocol, the PRP group received more injections than the HA group (PRP 3.2±1.2 vs HA 1.7±0.9, $p < 0.001$). Similar adverse effects occurred in both groups.

The patients of the HA group experienced more than 4-fold higher odds for arthroplasty rate (36.0% vs 5.3%) than patients in the PRP group (odds ratio [OR] 4.4, 95% [CI] 1.9–10.1; $p < 0.001$). A tendency to decrease the risk of knee arthroplasty was found in the Cox proportional hazard model, which included confounding factors identified by univariate analysis (HR=0.23, 95% CI, 0.05–1.05, p=0.058). (Figure 2) There was a statistically significant difference in risk for any arthroplasty between the groups in Kaplan-Meier curves. (Figure 3) The VAS for pain scores showed statistically significant differences at 6 months, 12 months, and at the last the follow-up favouring PRP over HA. The arthroplasty rate was significantly higher in the HA group even after propensity score matching (PRP n = 5 vs HA n = 16, $p = 0.010$). There were no statistically significant differences in ROM values at any of the follow-up points in the propensity-matched groups (all *p*-values > 0.05). A risk of any arthroplasty was detected between the propensity score matched groups in Kaplan-Meier curves. (Figure 4)

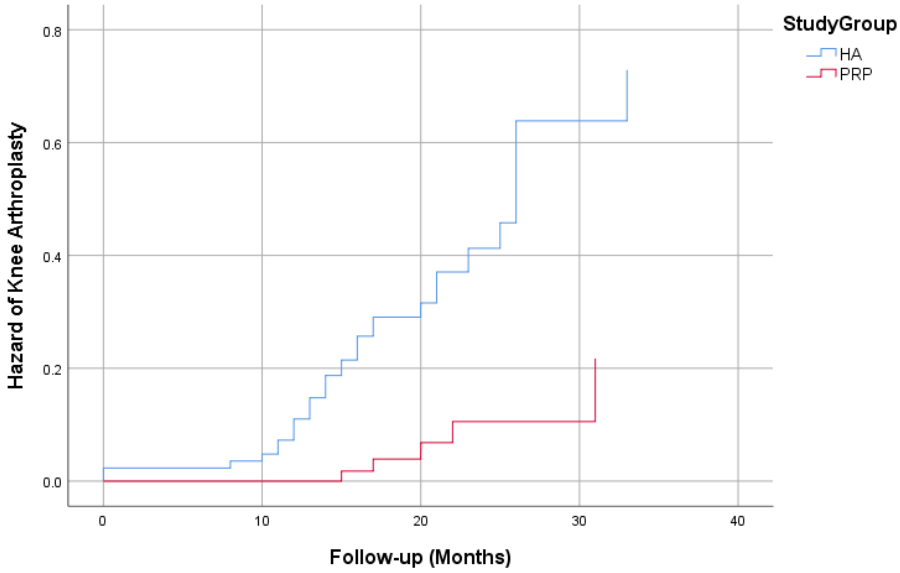


Figure 2. Cox proportional hazards estimates of knee arthroplasty according to intra-articular injections of HA or PRP for KOA (HR = 0.23, 95% CI, 0.05 – 1.05, p = 0.058).

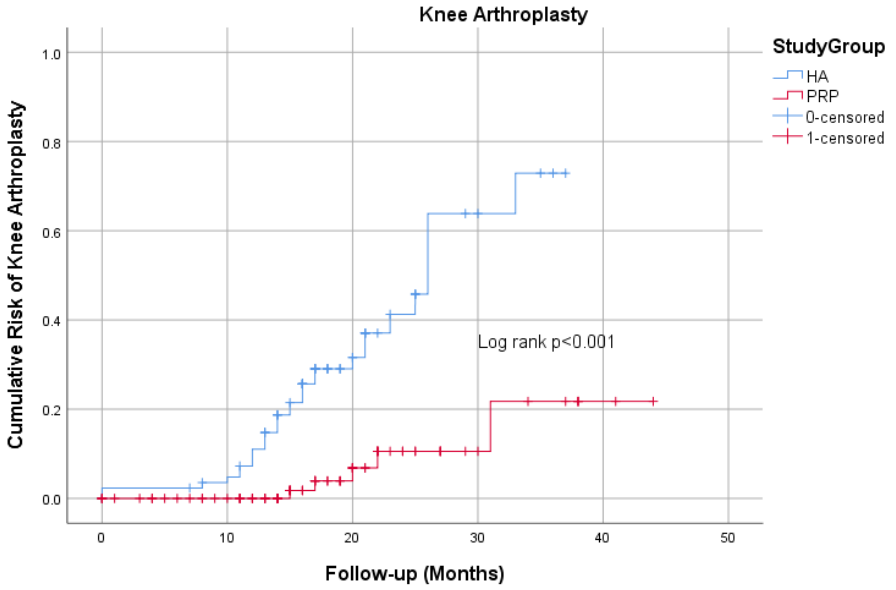


Figure 3. Kaplan-Meier curves of any arthroplasty occurrence for patients who underwent intra-articular injections of PRP or HA for KOA. A statistically significant difference ($p < 0.001$) is seen between the groups.

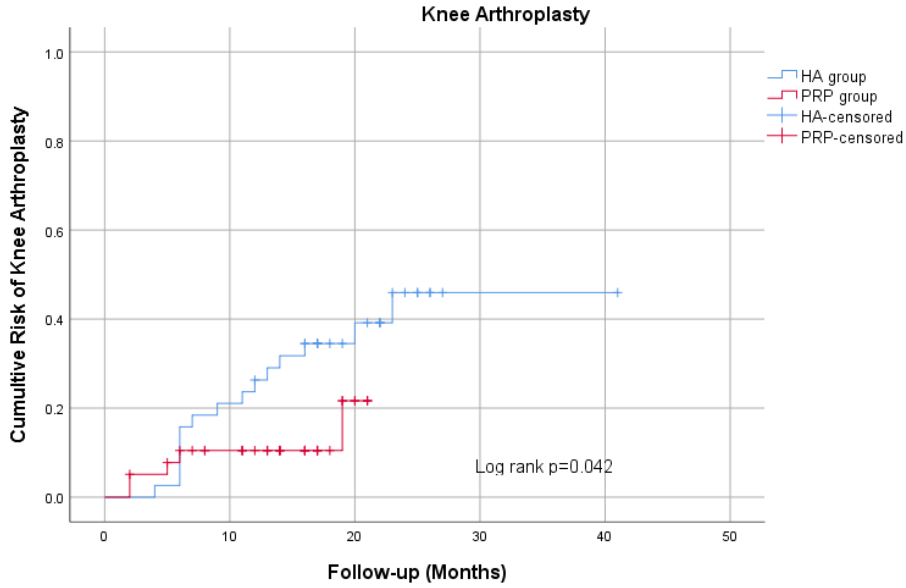


Figure 4. Kaplan-Meier curves of any arthroplasty occurrence for patients who underwent intra-articular injections of PRP or HA for KOA after propensity score matching. A statistically significant difference was found between the groups (p = 0.042).

5.1.2 Platelet-rich plasma in different stages of knee osteoarthritis (Study IV)

Study IV included 91 patients with symptomatic KOA of K-L grades 1 to 3. Patients received intra-articular injections of PRP to their knee and intergroup comparisons were made to determine whether an optimal stage of KOA for PRP treatments existed. Demographic data showed no differences between the groups A (K-L grade 1), B (K-L grade 2), and C (K-L grade 3), but the preintervention WOMAC overall score was significantly higher in intergroup comparison of Groups A and C (Group A WOMAC 23.0 ± 7.3; Group C WOMAC 34.5 ± 12.5, p = 0.013). There were no statistically significant differences in the baseline data between the Groups B and C (all p-values > 0.05). Table 11 has the most relevant results of Study IV, with only significant differences between Groups A and C in VAS for pain at 6 months and last follow-up, and WOMAC at the last follow-up.

Altogether, four adverse events were detected during the follow-up – one adverse event in Group B and three in Group C. Group A had none. The adverse event in Group B was prolonged pain for one week after the second injection, which resolved spontaneously. Group C's adverse events occurred after the second and third injections, causing prolonged pain for one week, before resolving spontaneously. Altogether, five patients underwent arthroplasty during the follow-up, one patient in Group B and four patients in Group C. No arthroplasties were detected in Group A.

The number of arthroplasties between the groups was statistically non-significant ($p > 0.05$): three patients had unicompartmental arthroplasty and two patients had TKA.

5.1.3 Platelet-rich plasma therapy in obese versus non-obese patients (Study V)

Study V included 91 patients with symptomatic KOA; the patients were divided into two groups according to their BMI: Group A, obese patients, BMI > 30 kg/m2; Group B, non-obese patients, BMI < 30 kg/m2). Both groups received intra-articular injections of PRP and had similar pre-interventional demographic data and PROM data, except for BMI, which was statistically significantly higher in Group A than Group B ($p < 0.05$). The mean K-L grade was similar in both groups, showing no statistically significant differences, as well as the number of patients in each K-L grade from 1 to 3.

Both groups showed improvement in the PROMs during the follow-up, but only the WOMAC overall score reached a statistically significant difference at the last follow-up favouring the non-obese group over the obese group (Group A 17.8 ± 18.8 vs Group B 10.5 ± 11.7, $p = 0.023$). (Figure 5) WOMAC was close to reaching statistical significance at 6 months ($p = 0.083$).

Neither ROM nor VAS values were significant throughout the follow-up. Obese patients had four more arthroplasties, and non-obese had one arthroplasty, but the difference was statistically non-significant between the groups (Group A 4 [11.8%] vs Group B 1 [1.8%], $p = 0.063$). The odds ratio (OR) for TKA was 3.5 (95% CI 0.3–40.1, $p = 0.553$), and for any arthroplasty, 7.5 (95% CI 0.8-69.8, $p = 0.085$), when comparing the two groups. Group B had 3 adverse events and Group A had a single adverse event. All the adverse events documented were prolonged pain with or without slight effusion in the knee joint, that resolved spontaneously within a week. No serious adverse events were detected.

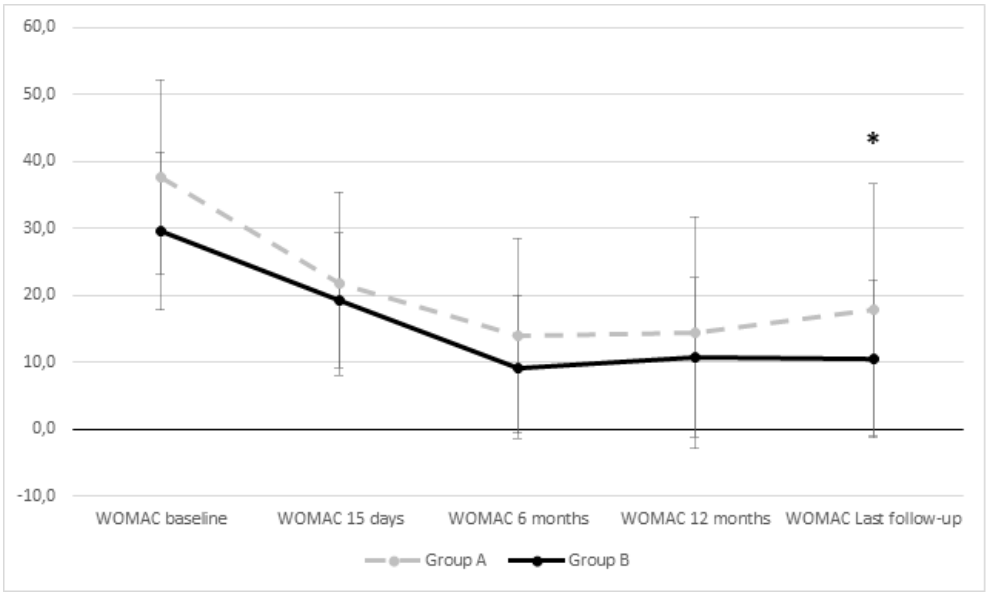


Figure 5. Mean WOMAC values of Groups A and B with ±1 S.D and statistically significant difference marked with an asterisk (*).

5.2 Platelet-rich plasma versus corticosteroid injections in rotator cuff tendinopathy (Study II)

Altogether, 75 patients were included in the analysis, 35 of whom received PRP injections and 40 CS injections. The most common endpoint before 18 months of follow-up was surgery. The demographic data showed statistically significant differences in sex ratio (PRP female to male ratio 28:7 vs CS 23:17, $p = 0.048$) and those having any comorbidities, which were statistically significantly higher in the CS group than the PRP group (PRP 7 [20%] vs CS 19 [47.5%], $p = 0.013$). No other statistically significant differences were detected between the groups in the demographic data. The only significant difference in the preintervention parameters was in the WORC emotion subscore between the two groups (PRP 189.7 ± 56.0 vs CS 146.7 ± 74.7, $p = 0.007$). The WORC lifestyle subscore trended towards statistical significance but did not reach it (PRP 253.3 ± 76.0 vs CS 222.9 ± 68.2, $p = 0.072$).

During the follow-up, there were no statistically significant differences between the two groups in WORC or any of its subscores, ROM or VAS at 6 months, 12 months, or 18 months (all $p > 0.05$). Likewise, there was no statistically significant difference in the number of shoulder area surgeries during the follow-up in either group, although the PRP group had fewer surgeries than the CS group (PRP 7 [20%] vs CS 11 [27.5%], $p = 0.589$). The PRP group had more injections than the CS

groups due to the study protocol, but no adverse events were detected in either group during the follow-up. The mean follow-up in Study II was over 21 months in both groups, with a statistically significant difference between the groups favouring the CS group over the PRP group (PRP 21.1 ± 8.7 vs CS 33.6 ± 16.3, $p < 0.001$).

The key finding of Study II was that PRP and CS seemed to produce similar effects in the long-term follow-up without a noticeable difference in PROMs, adverse events or patients undergoing surgical procedures.

5.3 Platelet-rich plasma injection versus conservative treatment in chronic tennis elbow (Study III)

Altogether, 55 patients were included in the analysis, 25 in the PRP group and 30 in the PT group. The only statistically significant differences in the demographic data between the groups were mean age (PRP 53.6 ± 8.4 versus PT 48.4 ± 9.9, $p = 0.045$) and sex-ratio (PRP F:M 11:14 vs PT F:M 23:7, $p = 0.013$). No statistically significant differences were detected between the groups in the baseline outcome scores. There was no statistically significant difference between the groups in the mean follow-up time (PRP 40.1 ± 6.5 vs PT 36.8 ± 15.5, $p = 0.329$); therefore, both groups had a mean follow-up of at least 36 months.

A statistically significant difference was detected in the number of elbow surgeries, with no surgeries in the PRP group and six surgeries in the PT group (PRP n = 0 / 0% vs PT n = 6 / 20%, $p = 0.027$). (Figure 6) During the follow-up statistically significant differences were found in VAS for pain, PRTEE, PRTEE function subscore, and DASH at 6 months, 12 months, and 24 months favoring the PRP group over the PT group. (Figure 6) The PRTEE function subscore did not reach a statistically significant difference at 24 months (PRP 4.8 ± 9.0 vs PT 11.1 ± 13.4, $p = 0.061$); a similar result was in DASH at 24 months (PRP 34.0 ± 8.0 vs PT 39.9 ± 12.5, $p = 0.052$). (Figure 6) Furthermore, there were no statistically significant differences in any of the parameters at 36 months of follow-up. (Figure 6) However, there was one adverse effect detected in the PRP group, when a patient-reported prolonged pain lasting up to 5 days after injection.

The key findings of Study III were that the PRP group had significantly better PROMs, in both functional scores and pain, for up to 24 months after the intervention. Only after 36 months of follow-up did the PT group reached similar PROM scores similar to the PRP group, but did not avoid surgical interventions, unlike the PRP group.

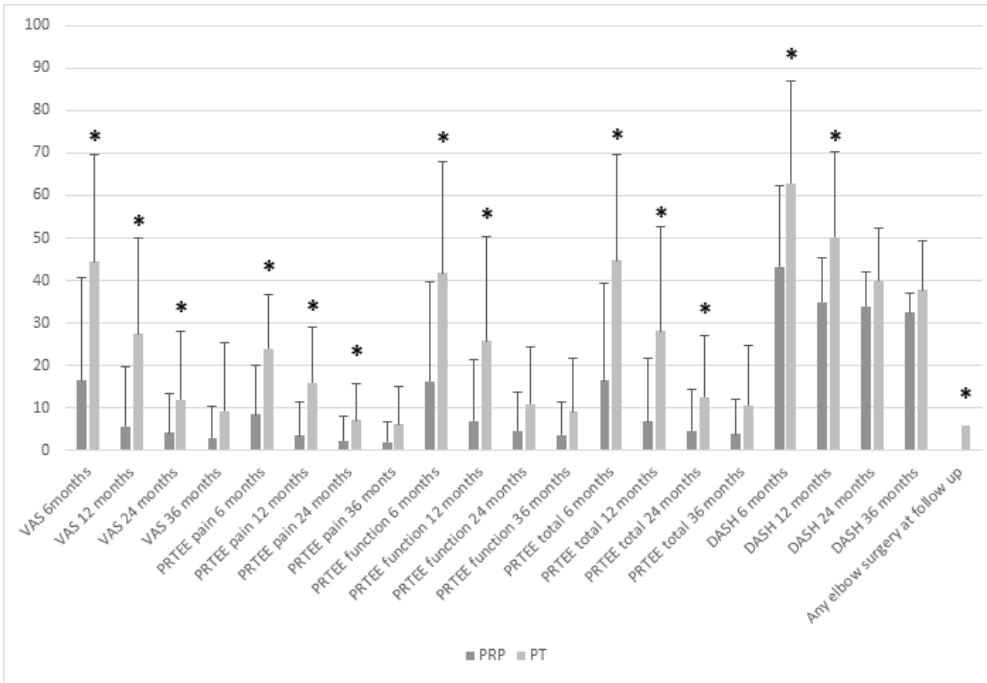


Figure 6. Comparison of post-interventional parameters and need for surgery in the two groups of patients with epicondylitis at 6, 12, 24 and 36-month follow-ups. Values are expressed in mean values with ±1 S.D; an asterisk (*) signifies a statistically significant difference favouring PRP over PT.

6 Discussion

This thesis provided insight into the possibility of postponing knee arthroplasty with PRP injections, the efficacy in different stages of KOA and the effect of BMI on PRP treatment success in KOA in long-term follow-up. Moreover, this thesis sought to investigate the long-term results of PRP injections relative to CS injection in RC tendinopathy and insight into how conventional PT exercises compare to PRP injection in chronic elbow epicondylitis. This work also adds to the safety profile of PRP, showing there were no major complications with PRP treatments regardless of the injection site or multiple injections, thus complementing previous literature. (Feltri et al., 2023)

The results for the KOA are consistent with some parts of the literature, in terms of symptom alleviation and emerging evidence of postponing arthroplasty. (Lin et al., 2019; Di Martino et al., 2019; Yurtbay et al., 2021; Migliorini et al., 2021; Li S et al., 2023; Berkani et al., 2022; Cheeva-Akrapan & Turajane, 2023; Sánchez et al., 2021) Conversely, however, they conflict with the part of the literature that depicts PRP as inferior to placebo and other injection treatments. (Dório et al., 2021; Han et al., 2021; Bennell et al., 2021; Lewis et al., 2022; Tschopp et al., 2023) As for the RC tendinopathy, the results are concurrent with the literature, in the mid-to long-term follow-up, with PRP having similar results as CS injections. (Jiang et al., 2023; Peng et al., 2023; Adra et al., 2023) The results for treating chronic elbow epicondylitis conflicted with the newest literature regarding PRP efficacy compared to placebo or overall efficacy. (Wong et al., 2022; Niemiec et al., 2022; Karjalainen & Buchbinder, 2023; Karjalainen T. et al., 2022; Hardy et al., 2021) Study III did not include a placebo and only compared PRP with PT exercises and avoidance of surgery, showing consistent results with the literature regarding avoiding surgery. (Hastie et al., 2018, Watts et al., 2020) Unfortunately, the literature search found no adequate studies comparing PT and PRP in elbow epicondylitis, leaving the comparison to the current literature open.

6.1 Platelet-rich plasma in mild to moderate knee osteoarthritis (Studies I, IV and V)

PRP efficacy was marginally better in mild K-L 1 KOA versus K-L 2 and 3 KOA, adhering to current literature regarding PRP being considered better and has a longer duration depending on how mild the KOA stage is. (Saraf et al., 2022, Jubert et al., 2017, Vilchez-Cavazos et al., 2023) BMI was not a major hindrance to the received benefit from the treatment, with non-obese (BMI < 30) benefitting only slightly more than obese (BMI >30) in long-term follow-up, with the results coinciding with the literature. (Niemiec et al., 2022) Finally, PRP seemed to reduce clinical symptoms of KOA better and postpone knee arthroplasty longer than HA, with similar results in the current literature. (Sánchez et al., 2021)

6.1.1 Platelet-rich plasma versus hyaluronic acid in mild to moderate knee osteoarthritis (Study I)

In Study I, PRP injections were superior to HA injections in the propensity score analysed series and the overall series. The PRP group demonstrated symptom alleviation and avoided knee arthroplasty more often than the HA group. Study I was the first propensity score-matched study to compare PRP and HA, demonstrating the differences in the risk of arthroplasty between autologous PRP versus HA in KOA in long-term follow-up. Sánchez et al.'s (2021) retrospective study found similar results to the PRP delaying the need for knee arthroplasty with a median delay of 4.1 years for all the patients analysed and up to 5.6 years when only responders to the treatment were analysed. A remarkable note is that arthroplasty was delayed for more than 10 years in over 15% of the patients. (Sánchez et al., 2021) Their study showed that up to 85.7% of patients avoid arthroplasty. (Sánchez et al., 2021) They suggested that new treatment cycles may be used to gain similar effects to the first cycle; thus, the initial effect may be prolonged even further. (Sánchez et al., 2021) Notably, the patients included in the Sánchez et al.'s (2021) study had moderate to end-stage KOA (Ahlbäck grades III–V and K-L grades 3–4) and were already on the verge of undergoing knee arthroplasty. Delaying knee arthroplasty is cost-efficient, and the median delay for TKA with HA is 10 months. However, similar studies regarding PRP are lacking; therefore, no definitive data is available, and thus further studies are warranted for PRP. (Berkani et al., 2022)

Neither Study I, nor previous studies found serious adverse events in treating patients with intra-articular PRP injections. (Hong et al., 2021) The only adverse effects detected in Study I were prolonged pain at the injection site for up to five days or mild effusion post-injection in PRP and HA groups. ROM values showed no statistically significant differences between the groups. Usually, ROM is reduced in

the end stage of KOA, which is probably why ROM showed no statistically significant differences, as both groups had only moderate KOA.

The WOMAC scores improved more in the PRP group than in the HA group, with a statistically significant difference that was also detectable in the long-term follow-up. The propensity score matching also revealed statistically significant differences at 6 months and the last follow-up points, still favouring PRP over HA. The VAS for pain score showed statistically significant results with and without propensity score matching that favoured the PRP group over the HA group at 6 months, 12 months, and at the last follow-up point. As stated, the results are concurrent with parts of the literature supporting PRP and conflicting with parts that do not. (Lin et al., 2019; Di Martino et al., 2019; Dório et al., 2021; Yurtbay et al., 2021; Han et al., 2021; Bennell et al., 2021; Migliorini et al., 2021; Lewis et al., 2022; Tschopp et al., 2023; Li S et al., 2023; Berkani et al., 2022; Cheeva-Akrapan & Turajane, 2023; Sánchez et al., 2021)

6.1.1.1 Strengths of Study I

Study I's strengths are the medium to long-term follow-up, meticulously collected demographic data, and the documentation of adverse events and end-points (arthroplasty), along with a reasonable number of patients. The propensity score matching reduced the initial differences in the pretreatment scores and demographics, improving the study's reliability. Multivariate regression combined with propensity score analysis controlled selection bias and treatment indication confusion. The reliability of the propensity score analysis increases when no hidden or unmeasured confounders are present. (Lonjon et al., 2017) By using the propensity score analysis, this study could consider factors not only affecting the outcome but also the factors that initially contributing to the selection for the type of injection used.

6.1.1.2 Limitations of Study I

Study I's limitations included the retrospective design, differences in the preintervention demographics, lack of knowledge of the amount of oral medication used, loss of over 50% of the patients during the propensity score analysis, and the number of injections the two groups received. As the difference in the number of injections was due to the treatment protocol inherent to the substances injected, such was deemed irrelevant. Propensity score produces a sort of randomisation, but it has its weaknesses and pitfalls, which may exclude some variables that may have affected the treatment selection and outcomes. However, true randomisation is still better; and would further reduce possible bias concerning patient selection. In the

overall series, the PRP group had more smokers, obese, and younger patients than the HA group; the patients HA group were older and had more comorbidities, higher WOMAC overall scores. The fluctuating symptoms of KOA may also affect the PROMs of the patients, as the symptoms may gradually fade regardless of intervention.

6.1.2 Platelet-rich plasma efficacy in different patient subgroups (Studies IV and V)

Studies IV and V explored the possibilities of more optimal patient selection when treating mild to moderate KOA with autologous intra-articular PRP injections. Both studies sought to find potential subgroups that would benefit more from PRP treatments, with Study IV concentrating on different stages of KOA, and Study V discerning the relevance of BMI regarding the treatment's efficacy. Study IV showed that K-L 1 to 3 patients with KOA improved their WOMAC scores and decreased their VAS scores drastically. Patients with K-L 1 graded KOA had no difference compared to K-L 2 graded KOA patients. The difference came between K-L 1 and 3, as K-L 1 KOA patients had better WOMAC in early and long-term follow-up and better VAS in medium and long-term follow-up. The results would confirm the previous evidence of PRP having a better impact on the early stages of KOA than the advanced stages, suggesting PRP to be not only a viable treatment throughout all stages of KOA but more optimal in the early stages. (Berkani et al., 2022) A small number of K-L 3 patients undergoing arthroplasty in Study IV would further promote this. As previously stated, the means to postpone arthroplasty are deemed cost-efficient, however, studies included in this thesis did not cover the cost-efficiency aspects of the treatments. Study V concluded that only the WOMAC score reached a statistical difference between non-obese and obese patients in long-term follow-up, while early and mid-term follow-up showed no difference. The difference, albeit statistically significant, is clinically minimal due to the difference in the last follow-up point and the mean follow-up was 13 months. Nevertheless, intra-articular PRP injections improved to PROMs regardless of BMI throughout the follow-up. The literature suggests obese patients would benefit more from PRP than HA. (Luo et al., 2020)

6.1.2.1 Strengths of Study IV and V

The strengths of Studies IV and V are medium to long-term follow-up, meticulously collected demographic data, adequate sample sizes, and the documentation of adverse events and end-points (arthroplasty). Both studies had comparable groups with marginal differences in demographics and initial PROMs. The study setting was

unique as both studies sought to find potential subgroups that may benefit more from the treatments to clarify decision making in clinical work.

6.1.2.2 Limitations of Study IV and V

The limitations of Studies IV and V included, the retrospective setting, lack of randomisation, and placebo control. Study IV showed a statistically significant difference between K-L 1 KOA patients and K-L 3 KOA patients in the WOMAC overall score, indicating that K-L 3 patients were significantly more symptomatic before injections were given. This difference in preintervention WOMAC score may cause a ripple effect that explains the difference between the groups in early and long-term follow-up. Such would also indicate that PRP meaningfully affected both groups in mid-term follow-up with only VAS being significantly different at 6 months, thus favoring K-L 1 patients over K-L 3 patients. In Study IV, the small number of K-L 1 patients is likely due to natural selection bias, as patients with early KOA may not even seek medical attention; therefore, finding these patients is difficult. This also raises a question: If severely symptomatic K-L 1 KOA patients are kind of a niche, is assuming that they would need injection therapy, given that symptoms are rarely long-lasting or debilitating, reasonable? One particularly interesting limitation rarely discussed in intervention studies is the fluctuating symptoms and natural course of the KOA. This may explain why PRP has had somewhat remarkable results in the earlier studies, inconsistencies in results with other injectables, and variability when compared to placebo.

6.1.3 Summary of Studies I, IV, and V

Based on this data, PRP injections are a safe and efficient treatment method in mild to moderate KOA regardless of BMI or severity of the KOA, and they reduce the odds of knee arthroplasty irrespective of a patient's group, especially in non-obese patients. PRP injections provided better results than HA injections in the medium to long-term follow-up and may be a viable alternative to HA injections especially when patients are not yet willing to undergo arthroplasty or other indications for arthroplasty have not yet been met. However, the critical view of PRP in literature and the limitations involved in this and previous studies, the rationale for injection therapies for KOA should be treated with caution; the possibility of natural fluctuation in KOA symptoms explaining some of the improvement seen with injection therapies, which should be addressed better in future studies.

6.2 Rotator cuff tendinopathy (Study II)

The PRP and CS groups had similar long-term results, with no significant differences detected in the WORC total, VAS, and ROM scores during any of the follow-up points. The results are mostly consistent with previous studies and meta-analyses of the matter, but the debate over efficacy continues. (Kwong et al., 2020; Jiang et al., 2023; Peng et al., 2023; Adra et al., 2023) Study II showed that similar results may be achieved with either treatment in RC tendinopathy in long-term follow-up. No adverse events were found during the follow-up and neither group had significantly more surgeries as the end-point of follow-up than the other. Notably, despite PRP possibly having comparable results to CS injections; it is not shown to be better than a placebo in the short- or long-term. (Karim et al., 2023; Rosso et al., 2023)

PRP injections have no documented significant adverse events in short- or long-term follow-ups, unlike CS injections, especially in the case of multiple CS injections. (Puzzitiello et al., 2020; Hurley et al., 2019) Patients who may be candidates for operative treatment of the shoulder area in the next 1 to 6 months should perhaps not be treated with CS, as prior CS injections increase the risk for complications and revision surgery. (Puzzitiello et al., 2020; Hurley et al., 2019) If patients are at risk of developing local systemic adverse events due to CS injection, perhaps PRP injection would be a better choice, especially if previous CS injections have not provided any significant help. PRP injections may also be repeated should the symptoms return. If no operative treatments are under consideration for the shoulder area in the near-future, or the risks involved in CS injection are considered acceptable, then the choice between the two options is probably indifferent. PRP may have an advantage over CS if adhesive capsulitis is present or if the progression of an RC tear is undesirable, but evidence of this is based on one study, and its possible clinical relevance is yet to be determined. (Tanpowpong et al., 2023; Feltri et al., 2023; Zhang et al., 2022) Despite the injection treatment chosen, concurrent PT is strongly recommended. (Rosso et al., 2023; Jiang et al., 2023)

6.2.1 Strengths of Study II

Study II's strengths were a reasonable number of patients and long-term follow-up. Several imaging modalities were involved, which helped immensely screening patients. Inclusion and exclusion criteria were comprehensive, along with meticulous documentation of demographic and clinical data of the patients. An experienced orthopaedist performed the injections using anatomical landmarks and aspiration before administering the injection.

6.2.2 Limitations of Study II

Study II's limitations were concurrent PT, retrospective study design, lack of comprehensive rotational ROM data, lack of randomisation, lack of placebo control, difference in comorbidities, female-to-male sex ratio between the groups, oral pain medication, and lack of US guidance during the injections. Due to the study design, inherent limitations such as lack of randomisation or injection technique could not be affected. However, the lack of US guidance during the injection is not necessarily a significant limitation, as studies show there is little clinical difference between US-guided and anatomical landmark-guided injections; however, US-guided injections may be more accurate than landmark guided. (Bhayana et al., 2018) Study II concentrates on the long-term results, which is why the relevance of the lack of a placebo control group is diminished, due to the placebo effect being detectable on average at 1 month of follow-up but not after that, according to Lin et al.'s (2019) study.

The incomplete rotational ROM not included in Study II leaves a blind spot in the clinical interpretation of the results. Concurrent PT is not necessarily a limitation, as both groups share the same protocol. PT may also be considered an essential part of the managing shoulder disorders, and excluding it from the design would be foolish. PT may explain some of the changes seen in the PROMs during the follow-up, but since the same protocol was applied to both groups, the effect should be similar. It is also worthwhile to consider that sometimes injection therapy or analgesics may help the patient even begin the PT. The oral pain medication the patients had could have lasted for a month and would unlikely show any significant effects beyond that. If any such effect would linger, it would probably be similar in both groups but may, nevertheless, lead to intergroup deviation of the results. The confounding factor of a higher female-to-male sex ratio may explain the lower mean pretreatment WORC emotions sub-score of the CS group.

We analysed several PROMs to evaluate the clinical effects of the treatments to address possible information bias. Selection bias is another possibility, and to address that the rationale for injection treatment was that the patient did not have any condition or disease that required surgical intervention at that point. The injection therapy was merely the next step in conservative treatment with no specific protocol for selection other than the patient deciding whether to try CS or PRP injection. The possibility for selection and information bias remains.

6.2.3 Summary of Study II

In light of Study II, PRP may be considered a viable alternative option for CS in RC tendinopathy due to its comparable effects, but without significant adverse effects. However, according to the literature, clear evidence for superiority over placebo or

CS is missing; therefore, any recommendations for using PRP on larger scale cannot be made. (Rosso et al., 2023; Pang et al., 2023) Since no single injection therapy seems significantly better than others, and there is a lack of quality RCT studies with placebo comparison, injection treatments in general for RCS should be treated with caution and perhaps be reserved as a desperate measure of conservative treatment or even avoided in clinical practice.

6.3 Chronic elbow epicondylitis (Study III)

Study III showed that PRP injection improves the patients' PROMs and provides an alternative option to surgery in chronic lateral epicondylitis compared to conventional continued PT exercises. The results align with some previous studies and contradict others on the overall efficacy of all the other treatment options; however, as the literature review stated, the literature does not support using PRP in lateral epicondylitis. (Linnanmäki et al., 2020; Karanasios et al., 2021; Wong et al., 2022; Karjalainen T. et al., 2021; Karjalainen & Buchbinder, 2023; Gedik et al., 2016; Lim et al., 2018) The PRP group fared better than the PT group in Study III, having significantly lower symptoms in PROMs and avoiding surgery more often, contradicting studies that Karjalainen et al. (2021) presented in a systematic review. Gedik et al.'s (2016) original study was available in the Turkish language, and, therefore, could not be referred to accurately, but Lim et al.'s (2018) study was available in English. Lim et al. (2018) concluded that PRP was superior to PT with correlation in MRI imaging, cytokine levels, and measured PROMs in 6 months of follow-up, but they lacked adequate double-blinding, reported their results with imprecision and did not include pain in their PROMs, which is why the results were downgraded in Karjalainen et al.'s (2021) review.

One adverse event was detected in the PRP group when one patient experienced prolonged pain and local swelling around the injection area. The symptoms resolved spontaneously within five days. No other adverse events were found. PRP injection can be considered a safe treatment option. No adverse events were detected in the PT group.

6.3.1 Strengths of Study III

Study III's strengths were the long-term follow-up, meticulously documented demographic data, use of several different PROMs, and rigorous inclusion and exclusion criteria. The follow-up was long enough to limit the possible early placebo effect. Study III was able to account realistically the natural course of elbow epicondylitis with the long-term follow-up; therefore, the effects of the treatments would be better shown and less masked by the natural course of the disease.

6.3.2 Limitations of Study III

Limitations were lack of randomisation, small sample size, the possibility of a placebo effect, baseline difference between the groups in age and sex ratio, and selection bias for the treatments. Also, comprehensive grip strength data was lacking. Due to the study's retrospective nature and lack of placebo control, biases involved in these matters were unavoidable.

Selection bias may be present, as patients chose the treatment they wanted, which may lead to patients with lower motivation choosing injection over PT, which also mean that truly motivated patients probably chose PT over injection; hence, the PT group may have reached the optimal possible effect from PT. The baseline demographics and PROMs were similar in both groups, with only mean age and sex ratio differences. Both groups had a mean age near 50, which is within the expected age range of epicondylitis, thus the age difference is probably not that significant of a factor.

The PRP group recovered faster than the PT group. The PT group reached similar PROM scores after 24 months of follow-up, yet VAS, PRTEE pain, and PRTEE total scores were still substantially higher in the PT group. Only after 36 months of follow-up were there no statistically significant differences between the groups in PROMs. The PRP group had significantly fewer surgeries than the PT group, the PRP group had no relapses. The results seem to persist even in long-term follow-ups. The lack of relapses may be an interesting factor for future studies when evaluating socio-economic factors such as sick leave length or desperate surgical interventions. A significant factor to consider is how long it took the PT group to reach PROMs similar to those of the PRP group.

While the results with PRP injections look good, it is worthwhile to consider that the disease's self-limiting nature may play a role in explaining some of the results for both groups, along with the placebo effect of a newly given treatment. (Ikonen et al., 2022) However, in some studies, the placebo effect may be detectable for 1 to 6 months and VAS for up to 12 months, making it strange that the differences between the groups stay until 36 months of follow-up, prompting the question of whether there is some effect to the treatment. (Gao et al., 2019) Patients included in Study III had chronic, long-lasting, symptomatic elbow epicondylitis that had not responded to conventional treatments, altough this is not the case in most studies, which may also explain the results. (Gao et al., 2019)

6.3.3 Summary of Study III

Study III suggests that an LR-PRP injection may significantly help chronic lateral epicondylitis when other conservative treatment options have not provided enough help despite the literature not supporting the results. Injection resolved symptoms

effectively, and patients avoided surgical intervention. If PRP is useful for chronic lateral epicondylitis, then it is certainly a better option than CS injection or surgery, which both are advocated to not be used for treating chronic elbow epicondylitis. Using PRP injections to treat chronic lateral epicondylitis would seem reasonable considering all the gained benefits, avoided risks, and socio-economic implications that faster symptom recovery may bring. Active patients may benefit the most as they may be able to return to sports earlier than with other treatments while avoiding the risks involved in surgery or CS injections if the situation is truly desperate. However, too many uncertainties are still involved with PRP treatments for any solid recommendation for its use to be made. Study III's results contradict to the current literature; therefore, they must be interpreted with caution. In summary, autologous LR-PRP treatments may have a silver lining in their efficacy for chronic elbow epicondylitis patients versus PT, but no large-scale evidence supports its use in clinical practice, and the literature and Study III's results should be interpreted with caution; more placebo-controlled studies are warranted for further clarification.

6.4 Controversies in platelet-rich plasma treatments

PRP treatments have faced significant criticism due to heterogenous study designs, different PRP products used, and suspicions of the pharmacy industry affecting various PRP studies. (Lu et al., 2023; Ta et al., 2023) One study concluded the pharmacy industry has not affected the integrity of significant RCT level PRP studies on KOA. (Ta et al., 2023**)** The logic of treating self-limiting diseases with a natural history of regressing to mean regarding symptoms, has been suggested as a potential explanation for previously reported results of PRP treatments. (Gao et al., 2019) The limitations and confounding factors of the studies have been reduced by more adequate documentation in the more recent literature, as PRP preparation, type of PRP used, and better study designs have reduced the heterogeneity.

6.4.1 Placebo and regression to mean in knee osteoarthritis and other degenerative musculoskeletal disorders

Intra-articular placebo may have more impact than a traditional "sugar pill" placebo. (Previtali et al., 2021; Fazeli et al., 2022) Intra-articular saline injections have been suggested as possibly producing a greater therapeutic effect on KOA patients than traditionally understood placebos due to the dilution of inflammation markers and lubrication of the joint space. (Previtali et al., 2021; Fazeli et al., 2022) This has been used as an argument to compare PRP to other injectables in KOA rather than saline. (Previtali et al., 2021; Fazeli et al., 2022) The placebo effect varies, but studies show

it may last somewhere between 1 to 6 months in KOA and even longer in lateral epicondylitis, especially in VAS scores up to 12 months; however, studies estimating the placebo effect duration also risk being affected by regression to the mean or a spontaneous resolution of symptoms. (Ikonen et al., 2022; Gao et al., 2019; Previtali et al., 2021; Fazeli et al., 2022) Therefore, other underlying factors in studies investigating injection therapies may cloud the actual placebo effect, and, in the case of intra-articular injections, perhaps some speculated theoretical therapeutic effect.

In the case of lateral epicondylitis, saline injections show gradual improvement over time, but no evidence indicates that saline would somehow affect the inflammation markers. Continuous improvement over time may be due to regressing to the mean or a spontaneous resolution of the disease. (Gao et al., 2019) Using saline as an adequate placebo control in lateral epicondylitis is justified. KOA is more difficult because studies hint that saline could be a therapeutic agent, but literature is scarce on this matter, warranting studies that investigate normal saline's potential role as a therapeutic agent. Shoulder studies involving placebo are scarce; therefore, the same speculations as with KOA have not been made. (Hurley et al., 2019)

Reflecting on the results, the potential placebo effect from any intra-articular injection may be more powerful and long-lasting with a duration of 1 to 6 months in KOA and maybe more in lateral epicondylitis. The effects of RC tendinopathy cannot be estimated accurately due to low evidence and the scarce number of studies. The placebo effect from any injection is attributed to general patient expectations from active treatment, speculated dilution of inflammatory markers from any extra fluid injected into the joint, concurrent disease regression to mean in KOA, and spontaneous resolution in lateral epicondylitis. All the studies of this thesis had a mean follow-up of over 12 months, partially eliminating the potential placebo effect from early to mid to late follow-up, when considering the longest of the follow-up points. However, this does not account for the regression to mean possibility as an explanation of the results; as both events run concurrently, the initial placebo effect may explain the differences between the groups in non-blinded, non-randomised, and non-placebo-controlled studies.

6.4.2 Injection technique

Previous studies have found only a small difference between US-guided and anatomical landmark-guided intra-articular injections in the knee and subacromial injections of the shoulder area regarding accuracy but a slightly larger difference in the elbow area. (Chernchujit et al., 2019; Luosujärvi, 2020; Keijsers et al., 2017; Rijs et al., 2021; Aly et al., 2015) In Finland, the technique used for injection is left up to the clinical practitioner; some may prefer US-guided injections but the most do not, and the current general practitioner's guide for injections advises one to use

anatomical landmarks. (Luosujärvi, 2020) An experienced orthopaedic surgeon, using anatomical landmarks, performed all the injections in Studies I to V. US-guided injections may be slightly more accurate than anatomical landmark-guided injections, which may cause some of the injections to miss their target. (Keijsers et al., 2017; Rijs et al., 2021, Aly et al., 2015) This would theoretically diminish the number of patients who would have received accurate treatment; however, there were, slightly fewer in Study II as the anatomical landmark-guided subacromial injections were deemed to have a comparable hit ratio to US-guided injections, and the number of CS injections missed would likely be in the same proportion to missed PRP injections. In Study III, the difference would be more significant as the control group received only PT and no injections; therefore, the theoretical diminishing effect would be in the PRP group only.

Studies I, IV, and V dealt with KOA, and injection accuracy in intra-articular injections for the knee was excellent with US-guided and anatomical landmark-guided injections. (Chernchujit et al., 2019; Luosujärvi, 2020) It is unlikely that any significant number of injections were missed in the HA or PRP groups, that would affect the results. If injections were missed, the effect would also likely be similar in both groups; therefore, the impact on the results would be similar in both groups.

In conclusion, injection techniques with anatomical landmarks may have played a role in interpreting the results. The risk of injection technique affecting the results is highest in Study III because the control group received no injections, causing the risk that only the PRP group will be affected by the missed injections. Studies I, II, IV, and V will likely have a lower risk of injection technique, thus impacting the results due to the high injection technique hit ratio and the control group being affected by the same limitation.

6.4.3 Type of platelet-rich plasma used

PRP used in the studies for this thesis was a commercial product by Glofinn Corporation, prepared according to the kit's instructions. According to the preparation protocol no means were taken to reduce the leukocyte count, making the final product LR-PRP as the centrifugation increases the leukocyte concentration. Different commercial kits vastly differ regarding to centrifugation spin speed, drawn blood used for preparation, the increase or reduction of white blood cell count, volume of the final product, time used for preparation, an open versus closed system, and final platelet count. (Collins et al., 2021) Basic science studies suggested LR-PRP may be more pro-inflammatory than LP-PRP, but clinical trials have shown LP-PRP to have perhaps a slight edge over LR-PRP in functional recovery; however, reported findings would need to be confirmed on a larger scale. (Jayaram et al., 2023; Abbas et al., 2022; Belk J W. et al., 2021; Chen et al., 2023; Di Martino A. et al.,

2022) Generally, LP-PRP is favoured over LR-PRP in KOA because basic science studies imply that in cartilage tissue avoiding catabolism is better than pursuing anabolism despite a lack of definitive evidence. (Jayaram et al., 2023; Abbas et al., 2022) Everts et al. (2023) suggested that PRP may stabilise the course of inflammation and facilitate healing by controlling the inflammatory response in KOA. The type of PRP used in Studies I, IV, and V will likely be insignificant concerning reported results, or if the PRP type affects the results, then the functional recovery may have been slightly better.

Basic science studies suggested that LR-PRP may have greater efficacy than LP-PRP in tendinopathy, by mediating the inflammatory response and ushering the tissue through a healing cascade while guiding it towards more normal tendon structure on molecular and cellular level. (Chalidis et al., 2023; Liu X et al., 2022; Shim et al., 2022; Muthu et al., 2021; Li S et al., 2022; Lana et al., 2019) Direct comparative studies for RC tendinopathy between LR-PRP and LP-PRP are missing, but other clinical studies suggest no difference in efficacy exists between the LR-PRP and LP-PRP for lateral epicondylitis. (Shim et al., 2022; Abbas et al., 2022; Niemiec et al., 2022; Yerlikaya et al., 2017) In light of basic science studies and clinical studies, the LR-PRP used for Studies II and III may have been optimal to facilitate healing.

Reports of mechanisms involved in natural healing cascade from basic science studies and may explain some controversies in various types of PRP used in previous studies, as it would hint that LR-PRP may not be optimal in KOA due to higher inflammation – promoting properties; in turn, it may be optimal in tendinopathy due to a higher promotion of inflammation to facilitate tendon repair mechanisms. However, more direct comparative studies are required in KOA and tendon pathologies to confirm or disprove this.

6.4.4 Adverse events related to platelet-rich plasma treatments

PRP injection treatment studies tend to report mostly minor adverse events such as local swelling, joint effusion, stiffness or prolonged pain after the injection or no adverse events at all. (Kim, J-H., et al., 2021; Xiong et al., 2023) No severe side effects have been detected compared to saline or HA, and the number of adverse events was similar in saline and HA patients. (Hong et al., 2021; Kim, J-H., et al., 2021) LR-PRP injections reportedly have more local adverse events than LP-PRP injections in OA patients due to the local inflammatory response of leukocytes. (Xiong et al., 2023) Patients involved in Studies I to V reported similar adverse events as described in the literature with no contradictions. The number of adverse events was scarce, and all the adverse events reported were local and transient.

6.5 Clinical implications and limitations

The evidence from current literature partly contradicts the results depicted in this thesis. Studies I to V showed PRP to be as effective, or more effective than conventional treatments for common degenerative orthopaedic diseases. Regarding KOA, PRP and avoiding arthroplasty were shown to be equal, or slightly better than HA in short- to medium-term follow-up. Postponing arthroplasty was perhaps the most novel discovery in Study I. PRP was equal to CS injection in RC tendinopathy, hinting at the possibility of avoiding the risk associated with CS injections while receiving the same benefit in the long term. A chronic elbow epicondylitis study showed remarkable results with PRP injections compared to conventional PT, showing that even long-lasting symptoms may be relieved with PRP in a relatively short time and with excellent results in long-term follow-up. Studies IV and V showed that PRP seems slightly more efficient in K-L grade 1 KOA versus K-L grade 3 KOA and that obesity does not significantly diminish the effects of PRP injections in KOA. All the studies confirmed that PRP is safe with only minor adverse events found, most likely to be associated with injections in general, rather than PRP. However, due to the retrospective nature of studies presented in this thesis and the lack of a placebo-controlled RCT setting, the risk of other factors explaining the results is possible, so further studies are needed to confirm or disprove the results.

This thesis provided interesting insights into the possibilities that PRP may offer. Certainly, delaying arthroplasty or quickly solving chronic elbow epicondylitis are sought-after results. No recommendations to justify or favour PRP in clinical practice can be made, due to low evidence and a lack of adequate placebo-controlled studies. While studies in this thesis showed excellent results with PRP injections, the evidence from this thesis alone is insufficient to support using PRP in clinical practice.

6.6 Future perspectives

PRP injections in KOA should be investigated further with more focus on placebo-controlled studies and the prospect of delaying arthroplasty. Should PRP be more effective than placebo or provide a delay in time to arthroplasty, it could be a cost-efficient treatment. OA is considered a progressive disease, that will eventually ruin the joint, if PRP turned out to be an effective treatment, it would be tremendous change in current recommendations for treating KOA. Another approach would be to study if recurrent PRP injections affect the natural history of OA. Further, if clear superiority over placebo is found, then a cost analysis of the injections versus arthroplasty would be of great interest, preferably with a sub-analysis of sick leave costs. Including a cost-efficiency analysis of treating patients nearing the end of their work career to see, if patients would avoid sick leave and arthroplasty altogether with

PRP treatments or undergo arthroplasty after they retire would be intriguing. Finally, the need for oral pain medication during the PRP treatment cycle would be interesting to study, as this raises the possibility of avoiding adverse effects associated with oral pain medication such as NSAIDs.

The RC tendinopathy studies should focus more on conservative treatment of the disease with US-guided injection therapies comparing PRP, CS, and placebo, preferably in a double-blinded RCT setting. An interesting aspect is the future of RC surgery and the implication of PRP in RC tears, whether traumatic or degenerative tears. Likewise, the possibility of PRP being a disease-modifying agent in KOA is intriguing but would require another long-term follow-up study. Concocting a shoulder study with enough confounding factors ruled out is difficult, and with so many details affecting the long-term health of the shoulder area, much time and effort will be required to properly study these matters.

Chronic lateral epicondylitis studies should focus on placebo-controlled settings to further prove or disprove the PRP's effectiveness. If PRP is proven to be above a mere placebo, then studies should focus on comparing current mainstream treatment options of PT exercises, oral pain medication, and the wait-and-see policy. In such cases, future studies should explore the socio-economic factors due to chronic lateral epicondylitis affecting mainly patients who still work or live active lives.

Altogether, the field of PRP studies should focus overall on placebo-controlled studies to definitively address the treatment's efficacy. The main criticism has been the lack of placebo-controlled studies, the foundation of proving non-inferiority and the effectiveness of a treatment. Further RCT studies will either seize the field and halt further studies or justify using PRP as a treatment option in selected diseases. Recent emerging studies have started addressing this problem, prompting the question: Should this field even be studied further, or is there enough evidence to say PRP is ineffective for degenerative joint or soft tissue diseases? While it has not been clearly stated in the literature, the entirety of injection treatments should be put into question. So, future studies should also clarify if any single injection treatment is in any way beneficial to patients versus a placebo.

Despite its controversial reputation and myriad conflicting literature, PRP is a potential treatment modality that should be studied until a definitive answer of its efficacy can be made. The most recent literature has changed how PRP is viewed as a potential treatment modality towards more critical reception, unlike previous studies that were reporting maybe even overly positive results of its efficacy. As the pendulum swings constantly year after year between positive and negative results, not making recommendations for everyday clinical use of PRP is wise. Simply too many uncertainties surround the matter. With this thesis, the pendulum swung towards positive once again, but the future tells if it swings back. Pursuing clinical truth and efficacy must continue until we unveil an unequivocal validation of PRP's

efficacy. Just as we eagerly delve into other new clinical inquiries, the same fervour should be devoted to PRP's potential meaning large-scale use of PRP in clinical work should be critically viewed because there is a risk it will not only be inefficient but cost a significant amount of funds from Finland's public healthcare system. In this thrilling journey, let us seize the opportunity to uncover the truth behind PRP's potential, aligning our actions with wisdom, responsibility, and the pursuit of excellence in health care.

7 Summary/Conclusions

This thesis summarises the use of PRP in common musculoskeletal disorders. The main findings are:

1. Autologous intra-articular PRP injections may provide long-term symptom relief and functional improvement in mild to moderate K-L 1 to 3 KOA and may postpone the need for arthroplasty.

2. Autologous PRP injections may provide equal symptom relief and functional improvement to CS injections in RC tendinopathy.

3. Autologous PRP injections may be viable option in chronic elbow epicondylitis versus conventional PT exercise with quick symptom resolution and reducing desperate surgical interventions.

4. Autologous intra-articular PRP injections were marginally better in mild K-L 1 KOA than in K-L 2 to 3 KOA.

5. Non-obese patients benefitted more from intra-articular PRP injections for mild to moderate KOA in long-term with lesser risk of arthroplasty than obese patients. BMI was not a major hindrance to the PRP's efficacy in short- to medium-term follow-up.

6. PRP was safe treatment regardless of multiple injections or different injection sites, with only minor adverse events detected.

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