

## Review

# Exploring Platelet-Rich Plasma Therapy for Knee Osteoarthritis: An In-Depth Analysis

Florin Nicolae Blaga <sup>1,2,†</sup>, Alexandru Stefan Nutiu <sup>1,2,†</sup> , Alex Octavian Lupsa <sup>1,2,†</sup>, Nicu Adrian Ghiurau <sup>1,2</sup> ,  
Silviu Valentin Vlad <sup>1,2,\*</sup> and Timea Claudia Ghitea <sup>3,\*</sup> 

<sup>1</sup> County Clinical Emergency Hospital of Oradea, 65 Gheorghe Doja Street, 410169 Oradea, Romania; blagafloirin86@yahoo.com (F.N.B.); alexandru\_nutiu@yahoo.com (A.S.N.); lupsalex@icloud.com (A.O.L.); ghiurau.adrian@yahoo.com (N.A.G.)

<sup>2</sup> Department of Surgical Specialties, Faculty of Medicine and Pharmacy, University of Oradea, 10 1st Decembrie Street, 410073 Oradea, Romania

<sup>3</sup> Pharmacy Department, Faculty of Medicine and Pharmacy, University of Oradea, 10 1st Decembrie Street, 410073 Oradea, Romania

\* Correspondence: silviu.vlad@didactic.uoradea.ro (S.V.V.); timea.ghitea@csud.uoradea.ro (T.C.G.)

† These authors contributed equally to this work.

**Abstract:** The use of platelet-rich plasma (PRP) in all medical fields is currently gaining popularity (1). PRP is a biological product that can be defined as a segment of the plasma fraction of autologous blood with a platelet concentration level above the baseline (2). The fact that it has uses in tissue regeneration and wound healing has caught the eye of orthopedic surgeons as well, as intra-articular treatments have continued to evolve. Its benefits in the treatment of different osteoarticular pathologies are of great interest in the evolving orthopedic community, targeting mostly knee osteoarthritis, meniscus and ligament injuries (3). The purpose of this review is to update the reader on the current uses of platelet-rich plasma (PRP) in the treatment of knee osteoarthritis pathology and to provide clinical feedback on its uses in the fields of orthopedic and sports medicine practice (4). We proceeded in studying 180 titles and abstracts eligible for inclusion. Compared to alternative treatments, PRP injections greatly improve the function of the knee joint.

**Keywords:** platelet-rich plasma; knee; osteoarthritis; treatment; orthopedic; intra-articular



**Citation:** Blaga, F.N.; Nutiu, A.S.; Lupsa, A.O.; Ghiurau, N.A.; Vlad, S.V.; Ghitea, T.C. Exploring Platelet-Rich Plasma Therapy for Knee Osteoarthritis: An In-Depth Analysis. *J. Funct. Biomater.* **2024**, *15*, 221. <https://doi.org/10.3390/jfb15080221>

Academic Editor: Silvia Panzavolta

Received: 12 July 2024

Revised: 2 August 2024

Accepted: 5 August 2024

Published: 9 August 2024



**Copyright:** © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Affecting over 300 million people, osteoarthritis is a degenerative joint disorder of the cartilage, targeting mostly women over 65 years, with 89% of the disorder site being the knee. Despite the increase in life expectancy, issues related to obesity are on the rise, along with an increasing incidence of sports-related injuries; consequently, the prevalence of knee pathologies continues to increase [1]. Hormonal imbalances [2], misuse of medications [3], inadequate rehabilitation following traumatic events or surgeries [4] and a lack of education about these conditions are all interconnected major factors [4].

Although widely studied and of great relevance in the modern medical world [5,6], the knee joint and the subsequent pathology that it can inherit still remain uncharted [7,8].

The presence of hyaluronic acid, along with its combined treatments involving extracorporeal shock wave therapy [9], has proven to be significantly more effective than monotherapy without hyaluronic acid [10].

Platelet-rich plasma (PRP) therapy has gained attention as a promising treatment for knee osteoarthritis (OA) due to its regenerative and anti-inflammatory properties. PRP is known for its ability to significantly reduce pain and improve knee function through the action of growth factors that promote tissue repair and cartilage regeneration [5,11]. Additionally, PRP's anti-inflammatory cytokines help alleviate joint swelling and inflammation, enhancing overall symptom relief. As an autologous treatment, PRP also presents

a minimally invasive alternative to surgical options, with a low risk of immune rejection or disease transmission [9,10].

Platelet-rich plasma (PRP) therapy has emerged as a noteworthy treatment for knee osteoarthritis (OA) due to its regenerative and anti-inflammatory effects [11]. PRP is effective for alleviating pain and enhancing knee function by leveraging growth factors that facilitate tissue repair and cartilage regeneration. It also helps reduce joint swelling and inflammation through its anti-inflammatory cytokines, offering significant symptom relief [12]. Additionally, as an autologous treatment, PRP is a minimally invasive option with a low risk of immune rejection or disease transmission, making it an appealing alternative to more invasive surgical procedures [13].

In addition to knee OA, PRP is used in various other medical areas. It aids in the treatment of chronic tendinitis, such as tennis elbow and Achilles tendinitis, by supporting tendon healing. In orthopedics, PRP promotes recovery from ligament injuries and enhances post-operative healing [14]. Its applications extend to dermatology as well, where it is utilized for skin rejuvenation and hair restoration, leveraging its regenerative properties to improve skin texture and stimulate hair growth. These diverse uses underscore PRP's broad potential for supporting recovery and regeneration across different medical conditions [14].

The purpose of this review was to take into account the most common osteoarticular pathologies, of which we chose to tackle three frequent diseases and to detail the current use of platelet-rich plasma, the physiological pathways of its constituents and the benefits they garner.

## 2. Materials and Methods

### 2.1. Search Strategy

We conducted a review of the characteristics of platelet-rich plasma used as intra-articular treatment for knee pathologies, particularly focusing on knee osteoarthritis.

This narrative review was conducted using three databases: Google Scholar, PubMed and MDPI. In order to identify the most useful articles, the search strategy included combined keywords such as “knee osteoarthritis”, “PRP treatment”, “osteoarthritis”, “knee pathology” and “platelet-rich plasma.” The databases were searched for studies published between 1974 and 2023.

The search strategy was designed to identify studies on the anti-inflammatory, analgesic and anti-aging effects of platelet-rich plasma treatments on knee pathologies, mostly knee osteoarthritis.

### 2.2. Study Selection and Eligibility Criteria

All electronically searched titles, selected abstracts and full-text publications were independently reviewed by a minimum of four reviewers. We included papers containing the keywords mentioned in our article. Although there was no restriction on the year of publication for the studies included, the majority of the papers were published after 2019.

Through database research, 236 records were identified. After removing 20 duplicates, as well as 36 irrelevant articles, we proceeded to study the remaining 180 titles and abstracts eligible for inclusion. Finally, we included 105 references that met the criteria of the study.

#### Inclusion Criteria

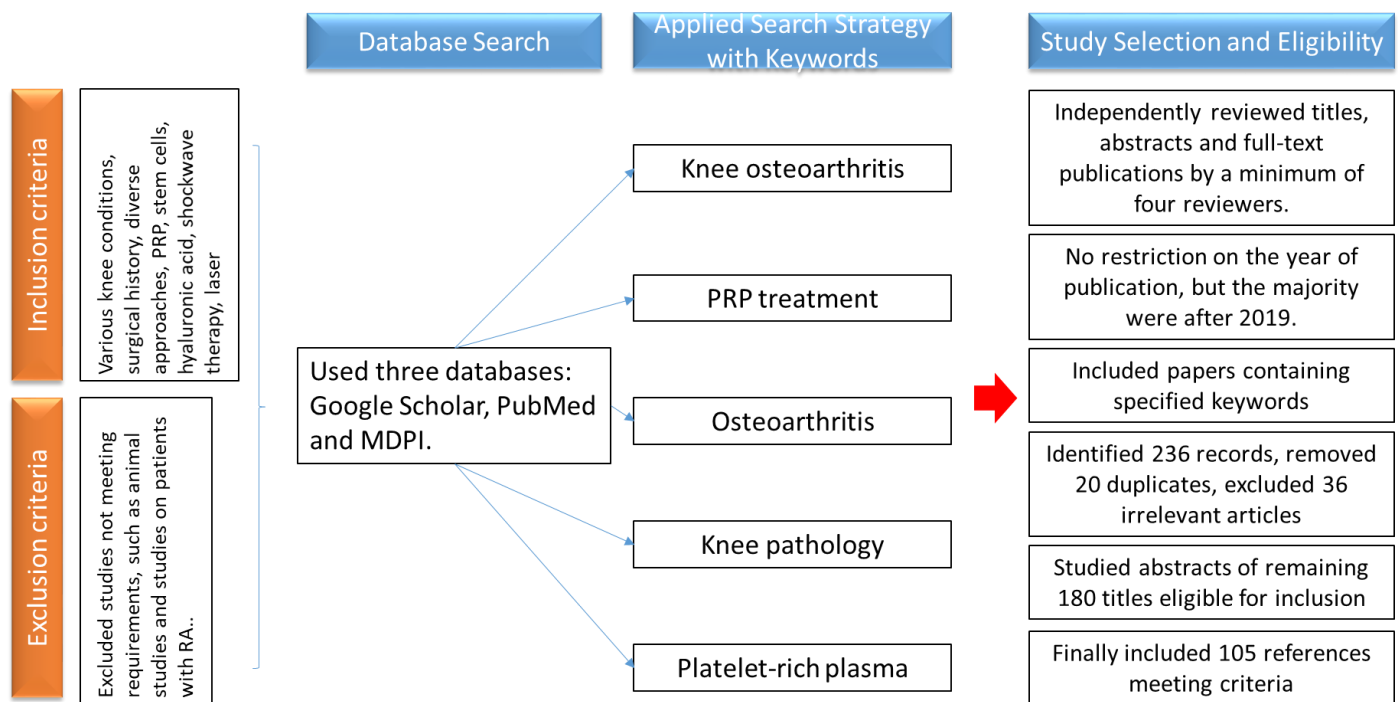
Inclusion criteria for articles encompassed a diverse range of pathologies, including primary and secondary osteoarthritis of the knee, osteochondritis dissecans, degenerative meniscal lesions and meniscal and/or ligamentous injuries. Papers in which patients underwent various surgical procedures involving the knee, such as meniscectomy, meniscus-sparing surgery, meniscus replacement, ligament reconstruction and knee osteotomy, were also included in the review.

The focus of the review extended to the treatment of knee osteoarthritis, osteochondritis, meniscal and ligament injuries, as well as the evaluation of these treatments. The

comprehensive review considered modern treatment methods, ranging from conservative and minimally invasive approaches to surgery, including the use of platelet-rich plasma, synovial mesenchymal stem cells, hyaluronic acid, extracorporeal shock wave therapy and high-intensity laser.

Exclusion criteria involved studies that did not meet the specified requirements, such as animal studies or those involving patients with rheumatoid arthritis. Additionally, papers published in languages other than English were excluded. Any disagreements regarding whether texts fit the inclusion or exclusion criteria were resolved through consensus. The search strategy is detailed in the flowchart shown in Figure 1.

**Review of platelet-rich plasma (PRP) properties for intra-articular treatment of knee pathologies, primarily knee osteoarthritis**



**Figure 1.** Flow chart.

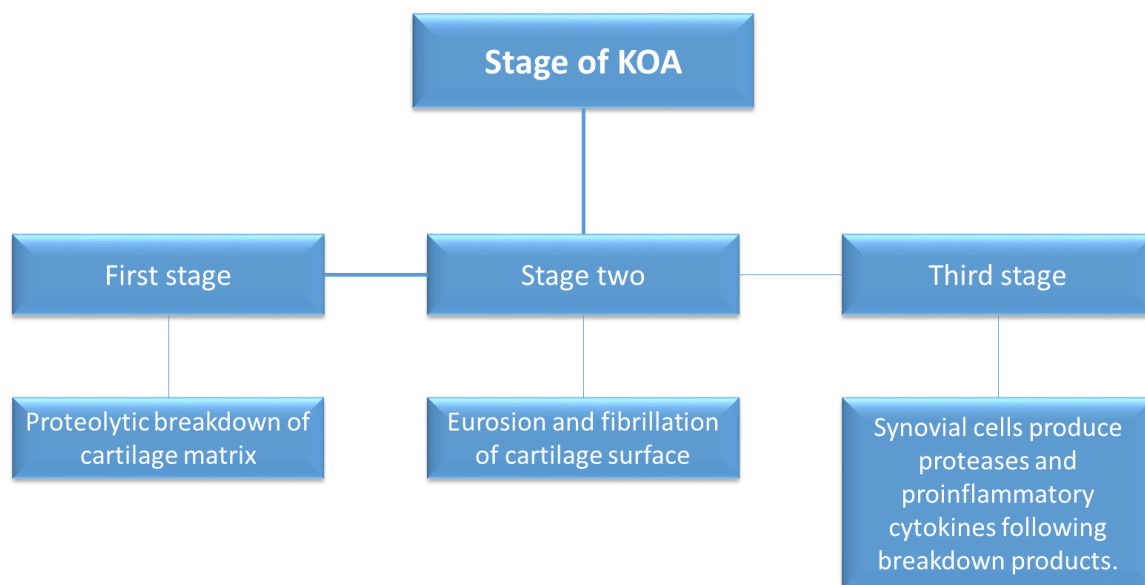
### 3. Results

#### *Knee Osteoarthritis*

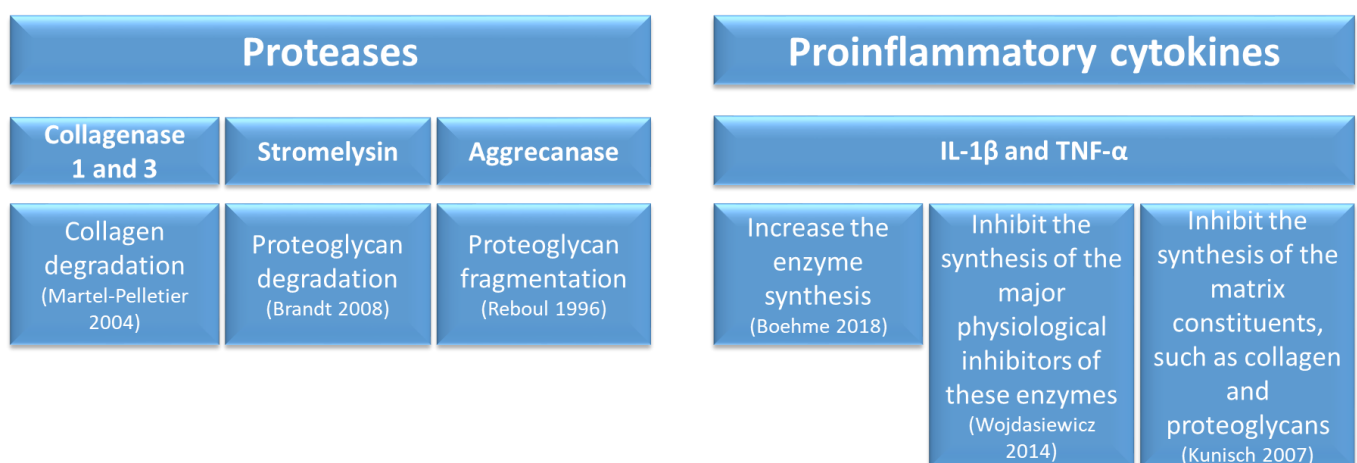
Osteoarthritis (OA), a prevalent knee pathology, affects approximately 300 million people globally, with increasing incidence in individuals over 65 years [15,16]. Knee OA, representing 89% of the global osteoarthritis segment, is particularly burdensome to the healthcare system [17]. Factors contributing to OA include age, obesity, genetic factors and mechanical stress [18,19]. The degenerative process occurs in three stages, involving proteolytic degradation, fibrillation and degradation of cartilage [20] (Figure 2).

The third phase includes collagen and proteoglycan degradation, increased pro-inflammatory enzymes and inhibited synthesis of matrix constituents [19–25] (Figure 3).

Age is a major contributor to OA, affecting the structural properties of cartilage's extracellular matrix [26]. OA leads to degeneration in articular cartilage, subchondral bone, connective tissue and abnormal joint metabolism [27,28]. Structural and molecular changes in the entire joint characterize OA [29]. Cartilage erosion, tissue loss, sub-chondral bone cyst formation and osteophytes are common [30]. Knee OA symptoms include pain, disability, stiffness, loss of function and swelling, as diagnosed via radiography, MRI or CT scan [31] (Figure 4).



**Figure 2.** Stages of KOA.

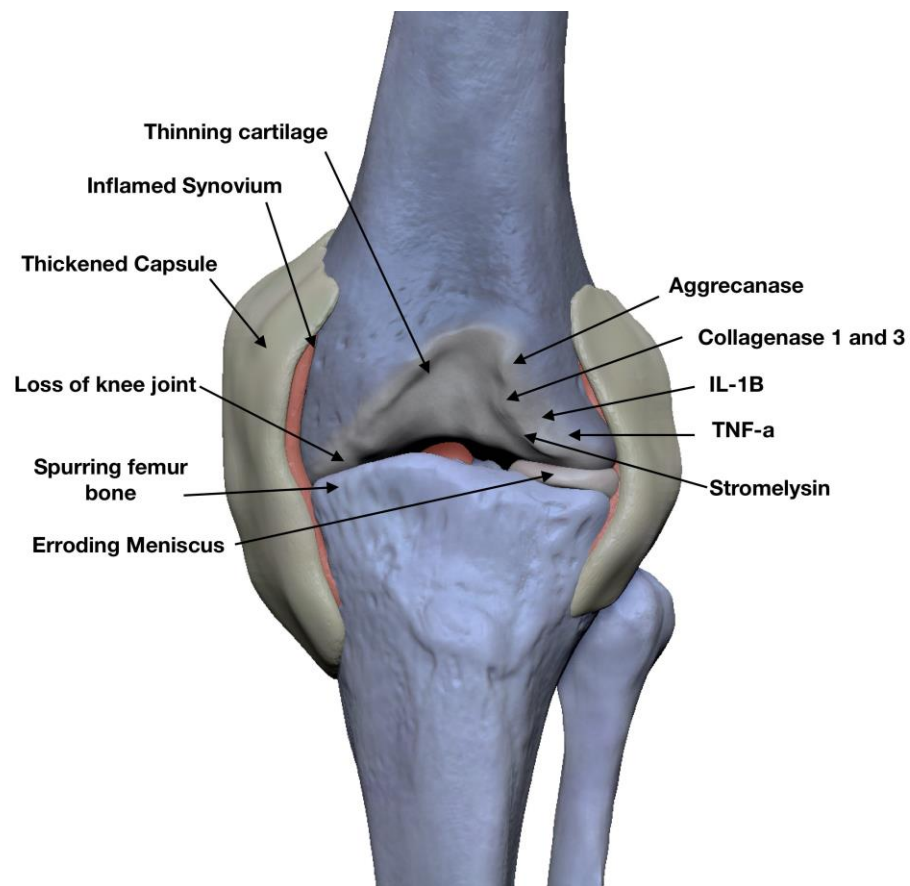


**Figure 3.** Third-stage KOA physiological pathways [19–25].

Degeneration of cartilage integrity and chondrocyte function alteration are major factors in OA knees. The cartilage tends to erode, and significant loss of tissue can appear due to the hyaline cartilage accumulating water, the reduction in proteoglycan levels and reduced cartilage stiffness. Formation of subchondral bone cysts are common, as well as osteophytes [30].

The main symptoms of knee osteoarthritis are pain, disability, stiffness, loss of function and swelling; confirmation of the diagnosis is performed via knee radiography, MRI or CT scan [31].

Ligament and meniscus injuries are prevalent in younger patients (25–50 years old), increasing the risk of OA in the long term [32,33]. Contrary to previous beliefs, these injuries may not always result from traumatic events, suggesting a connection with OA development [34–36]. Strategies to prevent and delay OA onset are crucial, especially in this demographic [37].



**Figure 4.** Structural and molecular changes in KOA. Adapted with permission of Bogdan-Viorel Leahu.

#### 4. Pharmacological Treatment of Knee Osteoarthritis

Knee osteoarticular (KOA) pathology is often treated from a short-term perspective, but considering patients' long-term experiences with KOA, it is crucial to emphasize long-term approaches [38,39]. Despite being cost-effective and simple, patient-controlled measures such as lifestyle changes and weight reduction are frequently overlooked [40,41]. Initial treatment for KOA aims for symptomatic relief [42], employing non-pharmacological and pharmacological methods. However, these approaches may offer short-lived benefits [43], with corticosteroid injections potentially worsening symptoms through cartilage degeneration [44,45]. The benefits of these kinds of treatments are usually short lived and the side effects that accompany especially injections with corticosteroids (cartilage degeneration) may further the symptoms even more [46].

##### 4.1. Platelet Rich Plasma

Platelets, or thrombocytes as they are also called, emerge from the bone marrow. Platelets appear as nucleated, discoid cellular elements of different sizes and, remarkably, are the least dense of all blood cells, at about 2  $\mu\text{m}$  in diameter. The normal number of platelets circulating in the blood stream of healthy individuals varies from 150,000 to 400,000 platelets per  $\mu\text{L}$  [47–49]. The primary process of the platelets is aggregation. Their role in hemostasis is ensured through 3 functions: adhesion, activation and aggregation. Vascular injuries initiate platelet activation, releasing specific factors that ensure coagulation through the secretory granules. Each platelet contains about 50–80 granules. There are three types of known secretory granules: dense granules, o-granules and lysosomes [50].

Although the initial understanding of platelets was that their role was solely that of a hemostatic agent, new research and advances in technology have resulted in their reevaluation. Studies have suggested that platelets have a role in inflammation, stem cell migration and proliferation and angiogenesis through the growth factors and cytokines that they contain [51].

When the platelets in PRP are activated, the P-granules go through degranulation and produce cytokines and growth factors that flow in the surrounding cellular space. For the use of PRP in common practice, the growth factors that are emitted and interest us most today are the vascular endothelial growth factor, transformative growth factor beta (TGF- $\beta$ 1), platelet-derived epidermal growth factor (PDEGF), insulin-like growth factor (IGF) and basic fibroblast growth factor (b-FGF or FGF-2). We highlight each of these growth factors that display several specific traits in Table 1 [32]. What is common among all and of great interest to us is their angiogenesis stimulation capacity [49,52,53].

**Table 1.** Most-studied growth factors and specific traits.

| Function                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Growth Factors                                     | Ref.                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|---------------------|
| Activates the production of KGF.<br>Regulates angiogenesis and wound contraction.<br>Promotes collagen synthesis, matrix and epithelialization.<br>Is responsible for the growth and differentiation of fibroblasts, myoblasts, osteoblasts, nerve cells, endothelial cells, keratinocytes and chondrocytes.<br>Acts as a mitogen for mesenchymal stem cells.<br>Stimulates the proliferation of myoblasts.                                                                                                                                                                                                                                                                                                                               | Basic Fibroblast Growth Factor (b-FGF)             | [54–59]             |
| Induces neovascularization by promoting proliferation and migration of macrovascular endothelial cells.<br>Promotes angiogenesis and participates in the formation of blood vessel lumen indirectly through the release of nitric oxide.<br>Initiates the regeneration of blood circulation and supports wound healing.<br>Activates the synthesis of metalloproteinase and is involved in the degradation of interstitial collagen types 1, 2 and 3.<br>Stimulates the chemotaxis of macrophages and neutrophils.                                                                                                                                                                                                                        | Vascular Endothelial Growth Factor (VEGF/VEP)      | [54–58,60]          |
| Stimulates endothelial angiogenesis.<br>Regulates the secretion of collagenase.<br>Stimulates epithelial and mesenchymal mitogenesis.<br>Supports wound healing by stimulating the proliferation of keratinocytes and dermal fibroblasts.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Platelet-Derived Epidermal Growth Factor (PDEGF)   | [55–57,60]          |
| Stimulates endothelial chemotaxis and angiogenesis.<br>Participates in the regulation of the balance between fibrosis and myocyte regeneration.<br>Inhibits the formation of osteoclasts and bone resorption.<br>Promotes chondrocyte proliferation and extracellular matrix synthesis, essential for cartilage repair.<br>Inhibits the proliferation of macrophages and lymphocytes.<br>Stimulates the chemotaxis of fibroblasts.<br>Increases the synthesis of type I collagen and fibronectin and regulates the secretion of collagenase.<br>Stimulates or inhibits endothelial, fibroblastic and osteoblastic mitogenesis.<br>Inhibits DNA synthesis in human fibroblasts.<br>Regulates the mitogenic action of other growth factors. | Transformative Growth Factor Beta (TGF- $\beta$ 1) | [54,55,57,58,60,61] |

Table 1. Cont.

| Function                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Growth Factors                   | Ref.    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|---------|
| Stimulates the growth of myoblasts and fibroblasts.<br>Activates the synthesis of collagenase and prostaglandin E2 in fibroblasts.<br>Regulates the metabolism of articular cartilage through increased synthesis of collagen and matrix osteon.<br>Stimulates cartilage growth, bone matrix formation and replication of preosteoblasts and osteoblasts.<br>Together with PDGF, it can increase the speed and quality of wound healing by activating collagen synthesis.<br>Mediates the growth and repair of skeletal muscles. | Insulin-like Growth Factor (IGF) | [55–60] |

#### 4.2. Platelet Rich Plasma Preparation

PRP, which is obtained through differential centrifugation, can be prepared in two ways: open (risking contamination) [59–61] and closed (using anticoagulants) [62]. Centrifugation yields a three-layered display, with ongoing debate about adding leukocytes to PRP [63–65]. Activation debates persist, with substances such as calcium gluconate initiating clotting for localized effects [66,67].

Optimal PRP concentration has been debated; current devices achieve 2–5 times baseline levels, but levels above 2.5 times may inhibit the desired action [68–70]. Growth factors released post-administration last up to a year, prompting multiple close-interval administrations due to platelet half-life [64].

Studies have explored carriers such as gelatin hydrogel, hydroxyapatite and chitosan PRP hybrids for enhanced growth factor efficiency and prolonged effects, showing promise in animal tests [71,72].

### 5. Benefits of PRP Treatment in Knee Pathology

The interest of orthopedic and sports medicine practices regarding PRP treatments for use in treating ligament, tendon and bone lesions is surging [73]. The growth factors dispersed by PRP play a major role in promoting cell recruitment, angiogenesis and proliferation, resulting in a reduction in inflammatory enzymes [73,74].

PRP has a role in improving the metabolic functions of injured structures by transmitting a regenerative signal that could affect the proliferation of stem cells, with a positive effect on chondrogenesis [61,75,76].

The growth factors contained in platelets contribute to cartilage proliferation, and when applied to chondrocytes, they tend to help with protein transcription, cell growth, cell migration and matrix synthesis as a whole. They signal the regenerative cascade and tissue healing, while containing the inflammatory response [77]. In joints that suffer from osteoarthritis, PRP affects local and infiltrating cells, synovial and endothelial cells, cartilage and bone cellular elements [78]. It may halt the advance of joint disease by mitigating inflammation and angiogenetic processes, while decreasing cartilage catabolism and increasing anabolism [51].

All of these successful PRP uses could easily imply that it has a use as a primary analgesic treatment by accelerating the proliferation of tenocytes, osteoblasts and mesenchymal stem cells [79,80]. By involving the whole joint complex, through the stimulation of cartilage proliferation, PRP injections can achieve clinical improvement and short-term remission of OA symptoms, even delaying the need for knee arthroplasty [81]. Although study results still are inconclusive, PRP treatments yield better results than hyaluronic acid or a placebo in all stages of knee OA [82]. Compared to HA injections, PRP offers more advantages in the conservative treatment of OA, such as better joint function and better long-term amelioration of symptoms; all patients have superior outcomes at their 3, 6 and 12 month evaluations when compared to injections with placebo, steroids or HA [83–85].

WOMAC scores are also lower (favorable) in all cases of PRP use when compared to HA or corticosteroid treatment [86].

Studies mostly tend to favor PRP treatment, as it is overall safe and delivers good outcomes, although it does have several disadvantages [32] (Table 2).

**Table 2.** Advantages and disadvantages of PRP treatment in the most recent studies.

| Criteria                                 | Benefits | Challenges | Other Considerations                                                               | Ref. |
|------------------------------------------|----------|------------|------------------------------------------------------------------------------------|------|
| Minimal Invasiveness                     | ✓        | ✓          | Does not involve any surgery, incisions or healing                                 | [84] |
| Rapid Preparation                        | ✓        | -          | Does not require any preservative                                                  | [84] |
| Compatibility with Patient Cells         | ✓        | -          | Use of patient cells without any further modification                              | [85] |
| Comprehensive Therapeutic Effects        | ✓        | -          | Can simultaneously reduce synovial inflammation, protect cartilage and reduce pain | [86] |
| Contaminant Reduction                    | ✓        | -          | Minimization of blood-borne contaminants                                           | [85] |
| Accelerated Recovery Time                | ✓        | -          | Recovery period reduced                                                            | [84] |
| Enhanced Biocompatibility                | ✓        | -          | Does not elicit an immune response                                                 | [84] |
| Morbidity at Injection Site              | -        | ✓          | Disadvantage only at the local level                                               | [86] |
| Standardization of Methods               | -        | ✓          | Does not exist                                                                     | [86] |
| Scar Tissue and Calcification            | -        | ✓          | Local risk                                                                         | [85] |
| Optimal Processing and Concentration     | -        | ✓          | Incompletely elucidated                                                            | [85] |
| Risk of Infections                       | -        | ✓          | Disadvantage only at the local level                                               | [86] |
| Risk of Allergic Reactions               | -        | ✓          | Disadvantage only at the local level                                               | [84] |
| Unknown Frequency and Volume             | -        | ✓          | Does not exist                                                                     | [85] |
| Contraindications for Certain Conditions | -        | ✓          | Incompletely known                                                                 | [86] |

✓ = presence of benefits/challenges, - = absence of benefits/challenges

Jang et al. conducted a review of 65 patients with knee osteoarthritis treated with a single intra-articular PRP administration. Clinical improvement was reported by most patients at 6 months, but the effects diminished one year after the injection [87]. In another study on 30 patients with knee chondropathy (Outerbridge I to III), Torrero et al. observed positive outcomes with a single intra-articular PRP administration, showing clinical improvement at the 6-month mark [88].

Hart et al. conducted a trial on 51 patients with chondromalacia grades II and III, spanning one year with nine autologous PRP injections, demonstrating significant clinical improvement [89]. In a randomized controlled trial by Patel et al. on bilateral osteoarthritis with 78 patients (156 knees), those receiving PRP injections (either a single dose or two injections) showed better results than the group receiving saline injections. The single dose with filtered concentrated white blood cells proved as effective as two PRP injections in terms of clinical improvement [90].

Filardo et al. compared two PRP preparation methods in 144 patients with osteoarthritis and degenerative cartilage lesions, finding significant clinical improvement in both groups at the one-year mark. The single-spinning method led to less ache and edema reported by patients [81].

Bansal et al. selected 150 randomized patients over three years, treating 75 with PRP and 75 with HA. Both groups showed significant improvement at one month, but the PRP-treated group retained benefits even at one year, while the HA-treated group showed a decline at subsequent controls (3, 6, 9 and 12 months) [69].

In total knee arthroplasty (TKA), the use of PRP has been documented in publications based on its effects, as shown in Table 3.

**Table 3.** Advantages and disadvantages of PRP treatment in TKA.

| Effects                                          | Without PRP | With PRP | Ref. |
|--------------------------------------------------|-------------|----------|------|
| Post-operative verbal pain scale                 |             | ✓        | [91] |
| Increased success rates                          |             | ✓        | [92] |
| Reduced blood loss                               | ✓           |          |      |
| Improved wound healing rate                      |             | ✓        | [93] |
| Better control of post-operative pain            |             | ✓        | [94] |
| Knee range of motion                             | ✓           | -        | [91] |
| Manipulation rates up to 3 months post-operative | ✓           | -        | [95] |
| The circumference of the operated joint          |             | ✓        | [96] |

PRP = Platelet-rich plasma, ✓ = presence of benefits/challenges, - = absence of benefits/challenges.

## 6. Discussion

Clinical studies provide compelling evidence suggesting the potential efficacy of PRP treatments for addressing osteoarticular degenerative joint pathology of the knee [31]. In comparison to alternative interventions, according to a 2017 study, PRP injections demonstrated notable improvement in knee joint function and served as a superior analgesic option [97]. The ease of preparation and administration, coupled with minimal need for extensive medical devices, positions PRP as a practical choice for regular use in orthopedic and sports medicine practices [98].

Several key mechanisms contribute to PRP therapy effectiveness in treating knee OA [32]. One of the primary mechanisms is the modulation of inflammation. PRP contains anti-inflammatory cytokines, such as interleukin-1 receptor antagonist (IL-1ra) and soluble tumor necrosis factor receptors, which inhibit pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- $\alpha$ ) [99]. This action reduces joint inflammation, swelling and pain, improving overall symptoms [100].

Another significant mechanism is tissue regeneration. PRP is rich in growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- $\beta$ ) and vascular endothelial growth factor (VEGF). Another significant mechanism is tissue regeneration. PRP is rich in growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- $\beta$ ) and vascular endothelial growth factor (VEGF) [101]. These growth factors stimulate cellular proliferation, differentiation and angiogenesis, which are crucial for repairing damaged tissues. TGF- $\beta$ , for instance, promotes chondrocyte proliferation and extracellular matrix production, aiding in cartilage repair. PDGF and VEGF enhance the formation of new blood vessels, improving nutrient and oxygen delivery to the damaged areas [102].

Additionally, PRP supports cartilage repair by influencing both anabolic and catabolic processes. It increases the production of cartilage matrix components, such as collagen type II and aggrecan, while decreasing the levels of matrix metalloproteinases (MMPs) that break down cartilage. This shift towards anabolic activity helps maintain and potentially restore cartilage integrity, which is essential for joint function [103].

Clinical evidence supports these mechanisms, with studies indicating significant improvements in pain and joint function following PRP treatment. For example, research by Smith et al. (2019) showed that PRP treatment led to meaningful improvements in clinical outcomes compared to other treatments, such as a placebo or hyaluronic acid injections, highlighting the effectiveness of PRP's biological action for managing knee OA [31].

However, according to Tey in 2022, the variability in PRP preparation modes, influenced by physician preference, poses a challenge in establishing universal guidelines applicable to the majority of patients [104]. Further research is essential in order to refine and define specific protocols that account for the diverse ways in which PRP is prepared. While ongoing studies show promise, the absence of standardized guidelines underscores the need for additional investigation to establish comprehensive and universally applicable protocols [105].

Despite its advantages, PRP treatment can cause several adverse effects. Common local reactions include pain, swelling and irritation at the injection site, which are generally mild and temporary. In rare cases, infections may occur if aseptic techniques are not strictly followed [106]. Some patients may experience a post-injection flare, marked by a temporary increase in pain and inflammation. Additionally, the lack of standardization in PRP preparation can lead to inconsistent outcomes, making the treatment's efficacy variable. On the other hand, PRP therapy offers promising benefits for knee osteoarthritis, including significant pain relief and improved joint function [107]. The growth factors in PRP, such as TGF- $\beta$  and VEGF, promote tissue repair and cartilage regeneration. Additionally, PRP's anti-inflammatory properties, mediated by cytokines such as IL-1 $\alpha$ , help reduce synovitis and joint swelling [108]. As a minimally invasive treatment, PRP poses a low risk of immune rejection or disease transmission since it uses the patient's own blood components [60].

The adaptability of PRP treatments to diverse clinical settings, coupled with its relative simplicity and safety profile, supports its potential as a valuable therapeutic option for managing knee osteoarthritis pathology [109,110]. Although precise guidelines are currently elusive, the encouraging results from recent studies contribute to the evolving understanding of PRP's role in knee joint health [111]. As research progresses, it is anticipated that a more nuanced and detailed framework for PRP application will emerge, offering clinicians clearer insights into its optimal use for improved patient outcomes.

PRP therapy offers regenerative potential and anti-inflammatory benefits by utilizing the patient's own blood components, making it a minimally invasive option with a low risk of immune reaction [112]. However, the variability in PRP preparation and uncertain long-term safety are notable drawbacks. By contrast, corticosteroid injections provide quick and effective pain relief and inflammation reduction, but their benefits are typically short-lived, and repeated use can lead to cartilage damage and other side effects [113].

Hyaluronic acid injections offer longer-lasting relief by improving joint lubrication but lack regenerative benefits and can be costly. Physical therapy is a non-invasive approach that focuses on muscle strengthening and joint stability, promoting long-term joint health [114]. However, its effectiveness depends on patient compliance and consistent participation. Surgical interventions such as arthroscopy and total knee replacement provide definitive treatment, particularly for severe cases, but are invasive and come with significant risks, including infection and lengthy recovery times [115].

PRP therapy typically costs between \$500 and \$2000 per injection, making it more expensive than corticosteroid (\$100–\$500) and hyaluronic acid (\$300–\$800) injections. Despite the higher cost, PRP offers potential long-term benefits through its regenerative effects, which can lead to sustained improvements in pain and function [116].

Corticosteroid injections provide quick, short-term relief but may require frequent administration due to diminishing efficacy and potential side effects. Hyaluronic acid injections offer longer-lasting relief compared to corticosteroids but lack the regenerative benefits of PRP [117].

Physical therapy, costing \$50–150 per session, is cost-effective for long-term joint health but requires patient commitment and time [118]. Surgical interventions are significantly more expensive, ranging from \$15,000 to \$50,000, and involve higher risks and recovery times. PRP may be a cost-effective option for patients seeking to delay or avoid surgery while potentially achieving longer-term relief [119].

The evolving understanding of knee pathologies, specifically the intricate interplay between aging, trauma and the onset of osteoarthritis (OA), has stimulated the exploration of diverse preventive strategies and prompted a reevaluation of conventional perspectives on causative factors. Continuous investigation and refinement of these concepts are imperative for the development of effective interventions using platelet-rich plasma (PRP) to alleviate the burden of OA on individuals and healthcare systems. Recent references emphasizing these aspects have become crucial for advancing our understanding and refining treatment approaches, laying the foundation for the utilization of PRP as a promising intervention for managing knee pathologies. This ongoing exploration is essential for tailoring PRP

applications to address the unique factors contributing to knee pathologies and offering targeted and innovative solutions for improved patient outcomes.

## 7. Conclusions

Clinical studies have yielded enough evidence to suggest that PRP treatments could be helpful for the osteoarticular degenerative joint pathology of the knee. Compared to alternative treatments, PRP injections greatly improve the function of the knee joint and exhibit improved analgesic properties.

The fact that preparation and administration of PRP is relatively easy, safe and does not require a vast array of medical devices makes it a good option for everyday use in orthopedic or sports medicine practices.

Considering the way that each preparation mode of PRP varies and depending on the physicians' preference, it is hard to choose an exact guideline that would apply to the vast majority of patients. More research has to be conducted in order to establish exact guidelines, but incoming studies and results are promising.

**Author Contributions:** Conceptualization, F.N.B. and S.V.V.; methodology, F.N.B., S.V.V., T.C.G., A.O.L. and N.A.G.; writing—original draft preparation, F.N.B., S.V.V., T.C.G., A.S.N., A.O.L. and N.A.G.; writing—review and editing, F.N.B., S.V.V., T.C.G. and A.S.N.; supervision, S.V.V. and N.A.G. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was partially funded by the University of Oradea and partially by the authors themselves.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Acknowledgments:** This paper is a result of the research conducted in elaborating the PhD thesis of Florin Nicolae Blaga.

**Conflicts of Interest:** The authors declare no conflicts of interest.

## References

1. Lespasio, M.J.; Piuizzi, N.S.; Husni, M.E.; Muschler, G.F.; Guarino, A.; Mont, M.A. Knee Osteoarthritis: A Primer. *Perm. J.* **2017**, *21*, 16–183. [[CrossRef](#)] [[PubMed](#)]
2. Hussain, S.M.; Cicuttini, F.M.; Alyousef, B.; Wang, Y. Female hormonal factors and osteoarthritis of the knee, hip and hand: A narrative review. *Climacteric* **2018**, *21*, 132–139. [[CrossRef](#)] [[PubMed](#)]
3. Bennell, K.L.; Hunter, D.J.; Hinman, R.S. Management of osteoarthritis of the knee. *BMJ* **2012**, *345*, e4934. [[CrossRef](#)] [[PubMed](#)]
4. Fregly, B.J.; Reinbolt, J.A.; Rooney, K.L.; Mitchell, K.H.; Chmielewski, T.L. Design of patient-specific gait modifications for knee osteoarthritis rehabilitation. *IEEE Trans. Biomed. Eng.* **2007**, *54*, 1687–1695. [[CrossRef](#)] [[PubMed](#)]
5. Messier, S.P.; Gutekunst, D.J.; Davis, C.; DeVita, P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. *Arthritis Rheum.* **2005**, *52*, 2026–2032. [[CrossRef](#)]
6. Gonçalves, S.; Gowler, P.R.; Woodhams, S.G.; Turnbull, J.; Hathway, G.; Chapman, V. The challenges of treating osteoarthritis pain and opportunities for novel peripherally directed therapeutic strategies. *Neuropharmacology* **2022**, *213*, 109075. [[CrossRef](#)]
7. Dulay, G.S.; Cooper, C.; Dennison, E. Knee pain, knee injury, knee osteoarthritis & work. *Best Pract. Res. Clin. Rheumatol.* **2015**, *29*, 454–461.
8. Nistor-Cseppento, C.D.; Gherle, A.; Negrut, N.; Bungau, S.G.; Sabau, A.M.; Radu, A.-F.; Bungau, A.F.; Tit, D.M.; Uivaraseanu, B.; Ghitea, T.C.; et al. The Outcomes of Robotic Rehabilitation Assisted Devices Following Spinal Cord Injury and the Prevention of Secondary Associated Complications. *Medicina* **2022**, *58*, 1447. [[CrossRef](#)]
9. Pellegrino, R.; Paolucci, T.; Brindisino, F.; Mondardini, P.; Di Iorio, A.; Moretti, A.; Iolascon, G. Effectiveness of High-Intensity Laser Therapy Plus Ultrasound-Guided Peritendinous Hyaluronic Acid Compared to Therapeutic Exercise for Patients with Lateral Elbow Tendinopathy. *J. Clin. Med.* **2022**, *11*, 5492. [[CrossRef](#)]
10. Pellegrino, R.; Brindisino, F.; Barassi, G.; Sparvieri, E.; de Sire, A.; Ruosi, C. Combined ultrasound guided peritendinous hyaluronic acid (500–730 Kda) injection with extracorporeal shock waves therapy vs. extracorporeal shock waves therapy-only in the treatment of shoulder pain due to rotator cuff tendinopathy. A randomized clinical trial. *J. Sports Med. Phys. Fit.* **2022**, *62*, 1211–1218. [[CrossRef](#)]
11. Balusani, P., Jr.; Shrivastava, S.; Pundkar, A.; Kale, P. Navigating the Therapeutic Landscape: A Comprehensive Review of Platelet-Rich Plasma and Bone Marrow Aspirate Concentrate in Knee Osteoarthritis. *Cureus* **2024**, *16*, e54747. [[CrossRef](#)] [[PubMed](#)]

12. Atwal, A.; Dale, T.P.; Snow, M.; Forsyth, N.R.; Davoodi, P. Injectable hydrogels: An emerging therapeutic strategy for cartilage regeneration. *Adv. Colloid Interface Sci.* **2023**, *321*, 103030. [[CrossRef](#)] [[PubMed](#)]
13. Abdollahi, A.; Emadi, E.; Hamidi Alamdari, D. Autologous platelet-rich-plasma injection and platelet-rich fibrin glue interposition for treatment of anal fistula resistant to surgery. *Gastroenterol. Hepatol. Bed Bench* **2023**, *16*, 292–296. [[CrossRef](#)] [[PubMed](#)]
14. Patil, P.; Jadhav, M.; Suvvari, T.K.; Thomas, V. Therapeutic uses of platelet-rich plasma (PRP) in sport injuries—A narrative review. *J. Orthop. Rep.* **2024**, *3*, 100287. [[CrossRef](#)]
15. Bec, C.; Rousset, A.; Brandin, T.; François, P.; Rabarimerarijaona, S.; Dumoulin, C.; Heleu, G.; Grimaud, F.; Veran, J.; Magalon, G.; et al. A Retrospective Analysis of Characteristic Features of Responders and Impaired Patients to a Single Injection of Pure Platelet-Rich Plasma in Knee Osteoarthritis. *J. Clin. Med.* **2021**, *10*, 1748. [[CrossRef](#)] [[PubMed](#)]
16. Glyn-Jones, S.; Palmer, A.J.; Agricola, R.; Price, A.J.; Vincent, T.L.; Weinans, H.; Carr, A.J. Osteoarthritis. *Lancet* **2015**, *386*, 376–387. [[CrossRef](#)]
17. Primorac, D.; Molnar, V.; Matišić, V.; Hudetz, D.; Jeleč, Ž.; Rod, E.; Čukelj, F.; Vidović, D.; Vrdoljak, T.; Dobričić, B.; et al. Comprehensive Review of Knee Osteoarthritis Pharmacological Treatment and the Latest Professional Societies' Guidelines. *Pharmaceuticals* **2021**, *14*, 205. [[CrossRef](#)]
18. Mobasher, A.; Batt, M. An update on the pathophysiology of osteoarthritis. *Ann. Phys. Rehabil. Med.* **2016**, *59*, 333–339. [[CrossRef](#)] [[PubMed](#)]
19. Martel-Pelletier, J. Pathophysiology of osteoarthritis. *Osteoarthr. Cartil.* **2004**, *12*, 31–33. [[CrossRef](#)]
20. Brandt, K.D.; Dieppe, P.; Radin, E.L. Etiopathogenesis of osteoarthritis. *Rheum. Dis. Clin. N. Am.* **2008**, *34*, 531–559. [[CrossRef](#)]
21. Reboul, P.; Pelletier, J.P.; Tardif, G.; Cloutier, J.M.; Martel-Pelletier, J. The new collagenase, collagenase-3, is expressed and synthesized by human chondrocytes but not by synoviocytes. A role in osteoarthritis. *J. Clin. Investig.* **1996**, *97*, 2011–2019. [[CrossRef](#)] [[PubMed](#)]
22. Boehme, K.A.; Rolauffs, B. Onset and progression of human osteoarthritis—Can growth factors, inflammatory cytokines, or differential miRNA expression concomitantly induce proliferation, ECM degradation, and inflammation in articular cartilage? *Int. J. Mol. Sci.* **2018**, *19*, 2282. [[CrossRef](#)] [[PubMed](#)]
23. Plaas, A.; Osborn, B.; Yoshihara, Y.; Bai, Y.; Bloom, T.; Nelson, F.; Mikecz, K.; Sandy, J. Aggrecanolytic in human osteoarthritis: Confocal localization and biochemical characterization of ADAMTS5–hyaluronan complexes in articular cartilages. *Osteoarthr. Cartil.* **2007**, *15*, 719–734. [[CrossRef](#)]
24. Wojdasiewicz, P.; Poniatowski, Ł.A.; Szukiewicz, D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. *Mediat. Inflamm.* **2014**, *2014*, 561459. [[CrossRef](#)] [[PubMed](#)]
25. Kunisch, E.; Gandesiri, M.; Fuhrmann, R.; Roth, A.; Winter, R.; Kinne, R.W. Predominant activation of MAP kinases and pro-destructive/pro-inflammatory features by TNF  $\alpha$  in early-passage synovial fibroblasts via TNF receptor-1: Failure of p38 inhibition to suppress matrix metalloproteinase-1 in rheumatoid arthritis. *Ann. Rheum. Dis.* **2007**, *66*, 1043–1051. [[CrossRef](#)]
26. Verzijl, N.; Bank, R.A.; TeKoppele, J.M.; DeGroot, J. Aging and osteoarthritis: A different perspective. *Curr. Opin. Rheumatol.* **2003**, *15*, 616–622. [[CrossRef](#)] [[PubMed](#)]
27. Neogi, T.; Zhang, Y. Epidemiology of osteoarthritis. *Rheum. Dis. Clin.* **2013**, *39*, 1–19. [[CrossRef](#)]
28. Wruck, C.J.; Fragoulis, A.; Gurzynski, A.; Brandenburg, L.-O.; Kan, Y.W.; Chan, K.; Hassenpflug, J.; Freitag-Wolf, S.; Varoga, D.; Lippross, S. Role of oxidative stress in rheumatoid arthritis: Insights from the Nrf2-knockout mice. *Ann. Rheum. Dis.* **2010**, *70*, 844–850. [[CrossRef](#)] [[PubMed](#)]
29. Dhillon, M.S.; Patel, S.; John, R. PRP in OA knee—Update, current confusions and future options. *Sicot J.* **2017**, *3*, 27. [[CrossRef](#)]
30. Adatia, A.; Rainsford, K.D.; Kean, W.F. Osteoarthritis of the knee and hip. Part I: Aetiology and pathogenesis as a basis for pharmacotherapy. *J. Pharm. Pharmacol.* **2012**, *64*, 617–625. [[CrossRef](#)]
31. Laver, L.; Marom, N.; Dnyanesh, L.; Mei-Dan, O.; Espregueira-Mendes, J.; Gobbi, A. PRP for Degenerative Cartilage Disease: A Systematic Review of Clinical Studies. *Cartilage* **2017**, *8*, 341–364. [[CrossRef](#)] [[PubMed](#)]
32. Szwedowski, D.; Szczepanek, J.; Paczesny, Ł.; Zabrzynski, J.; Gagat, M.; Mobasher, A.; Jeka, S. The Effect of Platelet-Rich Plasma on the Intra-Articular Microenvironment in Knee Osteoarthritis. *Int. J. Mol. Sci.* **2021**, *22*, 5492. [[CrossRef](#)] [[PubMed](#)]
33. Fernandes, G.S.; Sarmanova, A.; Warner, S.; Harvey, H.; Akin-Akinyosoye, K.; Richardson, H.; Frowd, N.; Marshall, L.; Stocks, J.; Hall, M.; et al. Knee pain and related health in the community study (KPIC): A cohort study protocol. *BMC Musculoskelet. Disord.* **2017**, *18*, 404. [[CrossRef](#)] [[PubMed](#)]
34. Rohren, E.M.; Kosarek, F.J.; Helms, C.A. Discoid lateral meniscus and the frequency of meniscal tears. *Skelet. Radiol.* **2001**, *30*, 316–320. [[CrossRef](#)]
35. Englund, M.; Roos, E.M.; Lohmander, L.S. Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: A sixteen-year followup of meniscectomy with matched controls. *Arthritis Rheum.* **2003**, *48*, 2178–2187. [[CrossRef](#)] [[PubMed](#)]
36. Englund, M.; Niu, J.; Guermazi, A.; Roemer, F.W.; Hunter, D.J.; Lynch, J.A.; Lewis, C.E.; Torner, J.; Nevitt, M.C.; Zhang, Y.Q.; et al. Effect of meniscal damage on the development of frequent knee pain, aching, or stiffness. *Arthritis Rheum.* **2007**, *56*, 4048–4054. [[CrossRef](#)] [[PubMed](#)]
37. Lohmander, L.S.; Englund, P.M.; Dahl, L.L.; Roos, E.M. The long-term consequence of anterior cruciate ligament and meniscus injuries: Osteoarthritis. *Am. J. Sports Med.* **2007**, *35*, 1756–1769. [[CrossRef](#)]
38. Charlesworth, J.; Fitzpatrick, J.; Perera, N.K.P.; Orchard, J. Osteoarthritis—a systematic review of long-term safety implications for osteoarthritis of the knee. *BMC Musculoskelet. Disord.* **2019**, *20*, 151. [[CrossRef](#)]

39. Ghitea, T.; Vlad, S.; Birle, D.; Tit, D.; Lazar, L.; Nistor-Cseppento, C.; Behl, T.; Bungau, S. The influence of diet therapeutic intervention on the sarcopenic index of patients with metabolic syndrome. *Acta Endocrinol.* **2020**, *16*, 470–478. [\[CrossRef\]](#)
40. Jenkinson, C.M.; Doherty, M.; Avery, A.J.; Read, A.; Taylor, M.A.; Sach, T.H.; Silcocks, P.; Muir, K.R. Effects of dietary intervention and quadriceps strengthening exercises on pain and function in overweight people with knee pain: Randomised controlled trial. *BMJ* **2009**, *339*, b3170. [\[CrossRef\]](#)
41. Gersing, A.S.; Schwaiger, B.J.; Nevitt, M.C.; Joseph, G.B.; Chanchek, N.; Guimaraes, J.B.; Mbapte Wamba, J.; Facchetti, L.; McCulloch, C.E.; Link, T.M. Is Weight Loss Associated with Less Progression of Changes in Knee Articular Cartilage among Obese and Overweight Patients as Assessed with MR Imaging over 48 Months? Data from the Osteoarthritis Initiative. *Radiology* **2017**, *284*, 508–520. [\[CrossRef\]](#)
42. Fransen, M.; McConnell, S. Exercise for osteoarthritis of the knee. *Cochrane Database Syst. Rev.* **2008**, *9*, Cd004376. [\[CrossRef\]](#)
43. Fransen, M.; McConnell, S. Land-based exercise for osteoarthritis of the knee: A metaanalysis of randomized controlled trials. *J. Rheumatol.* **2009**, *36*, 1109–1117. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Ringdahl, E.; Pandit, S. Treatment of knee osteoarthritis. *Am. Fam. Physician* **2011**, *83*, 1287–1292. [\[PubMed\]](#)
45. Alrushud, A.S.; Rushton, A.B.; Kanavaki, A.M.; Greig, C.A. Effect of physical activity and dietary restriction interventions on weight loss and the musculoskeletal function of overweight and obese older adults with knee osteoarthritis: A systematic review and mixed method data synthesis. *BMJ Open* **2017**, *7*, e014537. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Losina, E.; Weinstein, A.M.; Reichmann, W.M.; Burbine, S.A.; Solomon, D.H.; Daigle, M.E.; Rome, B.N.; Chen, S.P.; Hunter, D.J.; Suter, L.G.; et al. Lifetime risk and age of diagnosis of symptomatic knee osteoarthritis in the US. *Arthritis Care Res.* **2013**, *65*, 703–711. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Soeken, K.L.; Lee, W.-L.; Bausell, R.B.; Agelli, M.; Berman, B.M. Safety and efficacy of S-adenosylmethionine (SAME) for osteoarthritis. *J. Fam. Pr.* **2002**, *51*, 425–430.
48. Raynauld, J.P.; Buckland-Wright, C.; Ward, R.; Choquette, D.; Haraoui, B.; Martel-Pelletier, J.; Uthman, I.; Khy, V.; Tremblay, J.L.; Bertrand, C. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: A randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* **2003**, *48*, 370–377. [\[CrossRef\]](#)
49. Alves, R.; Grimalt, R. A Review of Platelet-Rich Plasma: History, Biology, Mechanism of Action, and Classification. *Ski. Appendage Disord.* **2018**, *4*, 18–24. [\[CrossRef\]](#)
50. Thöml, H.; Diem, H.; Haeflrich, T. *Color Atlas of Hematology: Practical Microscopic and Clinical Diagnosis*; Thieme: New York, NY, USA, 2004.
51. Le, A.D.; Enweze, L.; DeBaun, M.R.; Dragoo, J.L. Current clinical recommendations for use of platelet-rich plasma. *Curr. Rev. Musculoskelet. Med.* **2018**, *11*, 624–634. [\[CrossRef\]](#)
52. Andia, I.; Abate, M. Platelet-rich plasma: Underlying biology and clinical correlates. *Regen. Med.* **2013**, *8*, 645–658. [\[CrossRef\]](#) [\[PubMed\]](#)
53. de Sire, A.; Lippi, L.; Mezian, K.; Calafiore, D.; Pellegrino, R.; Mascaro, G.; Cisari, C.; Invernizzi, M. Ultrasound-guided platelet-rich-plasma injections for reducing sacroiliac joint pain: A paradigmatic case report and literature review. *J. Back. Musculoskelet. Rehabil.* **2022**, *35*, 977–982. [\[CrossRef\]](#)
54. Edwards, S.L.; Lynch, T.S.; Saltzman, M.D.; Terry, M.A.; Nuber, G.W. Biologic and pharmacologic augmentation of rotator cuff repairs. *J. Am. Acad. Orthop. Surg.* **2011**, *19*, 583–589. [\[CrossRef\]](#)
55. Creaney, L.; Hamilton, B. Growth factor delivery methods in the management of sports injuries: The state of play. *Br. J. Sports Med.* **2008**, *42*, 314–320. [\[CrossRef\]](#) [\[PubMed\]](#)
56. Moshiri, A.; Oryan, A. Role of platelet-rich plasma in soft and hard connective tissue healing: An evidence based review from basic to clinical application. *Hard Tissue* **2013**, *2*, 6. [\[CrossRef\]](#)
57. Somani, R.; Zaidi, I.; Jaidka, S. Platelet Rich Plasma-A Healing Aid and Perfect Enhancement Factor: Review and Case Report. *Int. J. Clin. Pediatr. Dent.* **2011**, *4*, 69–75. [\[CrossRef\]](#)
58. Ahmad, Z.; Howard, D.; Brooks, R.A.; Wardale, J.; Henson, F.; Getgood, A.; Rushton, N. The role of platelet-rich plasma in musculoskeletal science. *JRSM Short. Rep.* **2012**, *3*, 1–9. [\[CrossRef\]](#)
59. Dhurat, R.; Sukesh, M. Principles and Methods of Preparation of Platelet-Rich Plasma: A Review and Author's Perspective. *J. Cutan. Aesthet. Surg.* **2014**, *7*, 189–197. [\[CrossRef\]](#)
60. Pavlovic, V.; Ciric, M.; Jovanovic, V.; Stojanovic, P. Platelet Rich Plasma: A short overview of certain bioactive components. *Open Med.* **2016**, *11*, 242–247. [\[CrossRef\]](#)
61. Ficek, K.; Kamiński, T.; Wach, E.; Cholewiński, J.; Cieszyński, P. Application of platelet-rich plasma in sports medicine. *J. Hum. Kinet.* **2011**, *30*, 85–97. [\[CrossRef\]](#)
62. Magalon, J.; Brandin, T.; Francois, P.; Degioanni, C.; De Maria, L.; Grimaud, F.; Veran, J.; Dignat-George, F.; Sabatier, F. Technical and biological review of authorized medical devices for platelets-rich plasma preparation in the field of regenerative medicine. *Platelets* **2021**, *32*, 200–208. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Arshdeep, M. Platelet-rich plasma in dermatology: Boon or a bane? *Indian J. Dermatol. Venereol. Leprol.* **2014**, *80*, 5.
64. Ehrenfest, D.M.D.; Rasmusson, L.; Albrektsson, T. Classification of platelet concentrates: From pure platelet-rich plasma (P-PRP) to leucocyte-and platelet-rich fibrin (L-PRF). *Trends Biotechnol.* **2009**, *27*, 158–167. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Dhillon, M.S.; Patel, S.; Bansal, T. Improvising PRP for use in osteoarthritis knee-upcoming trends and futuristic view. *J. Clin. Orthop. Trauma* **2019**, *10*, 32–35. [\[CrossRef\]](#)

66. Everts, P.A.; Brown Mahoney, C.; Hoffmann, J.J.; Schönberger, J.P.; Box, H.A.; Van Zundert, A.; Knappe, J.T. Platelet-rich plasma preparation using three devices: Implications for platelet activation and platelet growth factor release. *Growth Factors* **2006**, *24*, 165–171. [\[CrossRef\]](#)
67. Du, L.; Miao, Y.; Li, X.; Shi, P.; Hu, Z. A novel and convenient method for the preparation and activation of PRP without any additives: Temperature controlled PRP. *BioMed Res. Int.* **2018**, *2018*, 1761865. [\[CrossRef\]](#) [\[PubMed\]](#)
68. Cavallo, C.; Roffi, A.; Grigolo, B.; Mariani, E.; Pratelli, L.; Merli, G.; Kon, E.; Marcacci, M.; Filardo, G. Platelet-rich plasma: The choice of activation method affects the release of bioactive molecules. *BioMed Res. Int.* **2016**, *2016*, 6591717. [\[CrossRef\]](#) [\[PubMed\]](#)
69. Bansal, H.; Leon, J.; Pont, J.L.; Wilson, D.A.; Bansal, A.; Agarwal, D.; Preoteasa, I. Platelet-rich plasma (PRP) in osteoarthritis (OA) knee: Correct dose critical for long term clinical efficacy. *Sci. Rep.* **2021**, *11*, 3971.
70. Gupta, A.K.; Carviel, J. A mechanistic model of platelet-rich plasma treatment for androgenetic alopecia. *Dermatol. Surg.* **2016**, *42*, 1335–1339. [\[CrossRef\]](#)
71. Shen, E.C.; Chou, T.C.; Gau, C.H.; Tu, H.P.; Chen, Y.T.; Fu, E. Releasing growth factors from activated human platelets after chitosan stimulation: A possible bio-material for platelet-rich plasma preparation. *Clin. Oral. Implant. Res.* **2006**, *17*, 572–578. [\[CrossRef\]](#)
72. Dwivedi, G.; Chevrier, A.; Hoemann, C.D.; Buschmann, M.D. Freeze dried chitosan/platelet-rich-plasma implants improve marrow stimulated cartilage repair in rabbit chronic defect model. *Trans. Orthop. Res. Soc.* **2017**, *13*, 599–611. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Sundman, E.A.; Cole, B.J.; Karas, V.; Della Valle, C.; Tetreault, M.W.; Mohammed, H.O.; Fortier, L.A. The anti-inflammatory and matrix restorative mechanisms of platelet-rich plasma in osteoarthritis. *Am. J. Sports Med.* **2014**, *42*, 35–41. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Van Buul, G.M.; Koevoet, W.L.; Kops, N.; Bos, P.K.; Verhaar, J.A.; Weinans, H.; Bernsen, M.R.; Van Osch, G.J. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. *Am. J. Sports Med.* **2011**, *39*, 2362–2370. [\[CrossRef\]](#)
75. Chen, X.; Jones, I.A.; Park, C.; Vangness Jr, C.T. The efficacy of platelet-rich plasma on tendon and ligament healing: A systematic review and meta-analysis with bias assessment. *Am. J. Sports Med.* **2018**, *46*, 2020–2032. [\[CrossRef\]](#)
76. Kabiri, A.; Esfandiari, E.; Esmaeili, A.; Hashemibeni, B.; Pourazar, A.; Mardani, M. Platelet-rich plasma application in chondrogenesis. *Adv. Biomed. Res.* **2014**, *3*, 138. [\[CrossRef\]](#)
77. Kon, E.; Filardo, G.; Di Martino, A.; Marcacci, M. Platelet-rich plasma (PRP) to treat sports injuries: Evidence to support its use. *Knee Surg. Sports Traumatol. Arthrosc.* **2011**, *19*, 516–527. [\[CrossRef\]](#)
78. Mifune, Y.; Matsumoto, T.; Takayama, K.; Ota, S.; Li, H.; Meszaros, L.B.; Usas, A.; Nagamune, K.; Gharaibeh, B.; Fu, F.H.; et al. The effect of platelet-rich plasma on the regenerative therapy of muscle derived stem cells for articular cartilage repair. *Osteoarthr. Cartil.* **2013**, *21*, 175–185. [\[CrossRef\]](#) [\[PubMed\]](#)
79. Meheux, C.J.; McCulloch, P.C.; Lintner, D.M.; Varner, K.E.; Harris, J.D. Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review. *Arthroscopy* **2016**, *32*, 495–505. [\[CrossRef\]](#) [\[PubMed\]](#)
80. Ogino, Y.; Ayukawa, Y.; Kukita, T.; Koyano, K. The contribution of platelet-derived growth factor, transforming growth factor-beta1, and insulin-like growth factor-I in platelet-rich plasma to the proliferation of osteoblast-like cells. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* **2006**, *101*, 724–729. [\[CrossRef\]](#)
81. Filardo, G.; Kon, E.; Di Martino, A.; Di Matteo, B.; Merli, M.L.; Cenacchi, A.; Fornasari, P.M.; Marcacci, M. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: Study design and preliminary results of a randomized controlled trial. *BMC Musculoskelet. Disord.* **2012**, *13*, 229. [\[CrossRef\]](#)
82. Kanchanatawan, W.; Arirachakaran, A.; Chaijenkij, K.; Prasathaporn, N.; Boonard, M.; Piyapittayanun, P.; Kongtharvonskul, J. Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee. *Knee Surg. Sports Traumatol. Arthrosc.* **2016**, *24*, 1665–1677. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Tang, J.Z.; Nie, M.J.; Zhao, J.Z.; Zhang, G.C.; Zhang, Q.; Wang, B. Platelet-rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: A meta-analysis. *J. Orthop. Surg. Res.* **2020**, *15*, 403. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Migliorini, F.; Driessen, A.; Quack, V.; Sippel, N.; Cooper, B.; Mansy, Y.E.; Tingart, M.; Eschweiler, J. Comparison between intra-articular infiltrations of placebo, steroids, hyaluronic and PRP for knee osteoarthritis: A Bayesian network meta-analysis. *Arch. Orthop. Trauma Surg.* **2021**, *141*, 1473–1490. [\[CrossRef\]](#) [\[PubMed\]](#)
85. Moretti, L.; Maccagnano, G.; Coviello, M.; Cassano, G.D.; Franchini, A.; Laneve, A.; Moretti, B. Platelet Rich Plasma Injections for Knee Osteoarthritis Treatment: A Prospective Clinical Study. *J. Clin. Med.* **2022**, *11*, 2640. [\[CrossRef\]](#)
86. Huang, Y.; Liu, X.; Xu, X.; Liu, J. Intra-articular injections of platelet-rich plasma, hyaluronic acid or corticosteroids for knee osteoarthritis: A prospective randomized controlled study. *Orthopade* **2019**, *48*, 239–247. [\[CrossRef\]](#) [\[PubMed\]](#)
87. Jang, S.J.; Kim, J.D.; Cha, S.S. Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis. *Eur. J. Orthop. Surg. Traumatol.* **2013**, *23*, 573–580. [\[CrossRef\]](#) [\[PubMed\]](#)
88. Torrero, J.L.; Aroles, F.; Ferrer, D. Treatment of knee chondropathy with platelet-rich plasma. Preliminary results at 6 months of follow-up with only one injection. *J. Biol. Regul. Homeost. Agents* **2012**, *26*, 71s–78s. [\[PubMed\]](#)
89. Hart, R.; Safi, A.; Komzák, M.; Jajtner, P.; Puskeiler, M.; Hartová, P. Platelet-rich plasma in patients with tibiofemoral cartilage degeneration. *Arch. Orthop. Trauma Surg.* **2013**, *133*, 1295–1301. [\[CrossRef\]](#) [\[PubMed\]](#)
90. Patel, S.; Dhillon, M.S.; Aggarwal, S.; Marwaha, N.; Jain, A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: A prospective, double-blind, randomized trial. *Am. J. Sports Med.* **2013**, *41*, 356–364. [\[CrossRef\]](#)
91. Guerreiro, J.P.; Danieli, M.V.; Queiroz, A.O.; Deffune, E.; Ferreira, R.R. Platelet-rich plasma (PRP) applied during total knee arthroplasty. *Rev. Bras. Ortop.* **2015**, *50*, 186–194. [\[CrossRef\]](#)

92. Attia, S.; Narberhaus, C.; Schaaf, H.; Streckbein, P.; Pons-Kühnemann, J.; Schmitt, C.; Neukam, F.W.; Howaldt, H.-P.; Böttger, S. Long-Term Influence of Platelet-Rich Plasma (PRP) on Dental Implants after Maxillary Augmentation: Implant Survival and Success Rates. *J. Clin. Med.* **2020**, *9*, 391. [\[CrossRef\]](#) [\[PubMed\]](#)
93. Shu, H.; Huang, Z.; Bai, X.; Xia, Z.; Wang, N.; Fu, X.; Cheng, X.; Zhou, B. The Application of Platelet-Rich Plasma for Patients Following Total Joint Replacement: A Meta-Analysis of Randomized Controlled Trials and Systematic Review. *Front. Surg.* **2022**, *9*, 922637. [\[CrossRef\]](#) [\[PubMed\]](#)
94. Guerreiro, J.P.F.; Lima, D.R.; Bordignon, G.; Danieli, M.V.; Queiroz, A.O.; Cataneo, D.C. Platelet-Rich Plasma (PRP) and Tranexamic Acid (TXA) Applied in Total Knee Arthroplasty. *Acta Ortop. Bras.* **2019**, *27*, 248–251. [\[CrossRef\]](#)
95. Pace, T.B.; Foret, J.L.; Palmer, M.J.; Tanner, S.L.; Snider, R.G. Intraoperative Platelet Rich Plasma Usage in Total Knee Arthroplasty: Does It Help? *ISRN Orthop.* **2013**, *2013*, 740173. [\[CrossRef\]](#) [\[PubMed\]](#)
96. Kosev, P.; Sokolov, T.; Pavlova, I.; Valentinov, B.; Andonov, J.; Petrova, N. Platelet Rich Plasma (PRP) Application in Total Knee Arthroplasty (TKA). *J. IMAB—Annu. Proceeding Sci. Pap.* **2015**, *21*, 814–817. [\[CrossRef\]](#)
97. Li, T.; Li, Y.; Li, W.; Wang, X.; Ding, Q.; Gao, J.; Zhang, Y.; Zhuang, W. Impact of autologous platelet-rich plasma therapy vs. hyaluronic acid on synovial fluid biomarkers in knee osteoarthritis: A Randomized controlled clinical trial. *Front. Med.* **2023**, *10*, 1258727. [\[CrossRef\]](#) [\[PubMed\]](#)
98. Everts, P.; Onishi, K.; Jayaram, P.; Lana, J.F.; Mautner, K. Platelet-Rich Plasma: New Performance Understandings and Therapeutic Considerations in 2020. *Int. J. Mol. Sci.* **2020**, *21*, 7794. [\[CrossRef\]](#)
99. Karina, K.; Rosliana, I.; Rosadi, I.; Sobariah, S.; Christoffel, L.M.; Novariani, R.; Rosidah, S.; Fatkhurohman, N.; Hertati, Y.; Puspitaningrum, N.; et al. Phase I/II Clinical Trial of Autologous Activated Platelet-Rich Plasma (aaPRP) in the Treatment of Severe Coronavirus Disease 2019 (COVID-19) Patients. *Int. J. Inflam.* **2021**, *2021*, 5531873. [\[CrossRef\]](#)
100. Lacko, M.; Harvanová, D.; Slovinská, L.; Matuška, M.; Balog, M.; Lacková, A.; Špaková, T.; Rosocha, J. Effect of Intra-Articular Injection of Platelet-Rich Plasma on the Serum Levels of Osteoarthritic Biomarkers in Patients with Unilateral Knee Osteoarthritis. *J. Clin. Med.* **2021**, *10*, 5801. [\[CrossRef\]](#)
101. Amable, P.R.; Carias, R.B.; Teixeira, M.V.; da Cruz Pacheco, I.; Corrêa do Amaral, R.J.; Granjeiro, J.M.; Borojevic, R. Platelet-rich plasma preparation for regenerative medicine: Optimization and quantification of cytokines and growth factors. *Stem Cell Res. Ther.* **2013**, *4*, 67. [\[CrossRef\]](#)
102. Chen, M.; Jiang, Z.; Zou, X.; You, X.; Cai, Z.; Huang, J. Advancements in tissue engineering for articular cartilage regeneration. *Heliyon* **2024**, *10*, e25400. [\[CrossRef\]](#) [\[PubMed\]](#)
103. McClurg, O.; Tinson, R.; Troeberg, L. Targeting Cartilage Degradation in Osteoarthritis. *Pharmaceuticals* **2021**, *14*, 126. [\[CrossRef\]](#) [\[PubMed\]](#)
104. Tey, R.V.; Haldankar, P.; Joshi, V.R.; Raj, R.; Maradi, R. Variability in Platelet-Rich Plasma Preparations Used in Regenerative Medicine: A Comparative Analysis. *Stem Cells Int.* **2022**, *2022*, 3852898. [\[CrossRef\]](#) [\[PubMed\]](#)
105. Schwartz, A.M.; Farley, K.X.; Guild, G.N.; Bradbury Jr, T.L. Projections and epidemiology of revision hip and knee arthroplasty in the United States to 2030. *J. Arthroplast.* **2020**, *35*, S79–S85. [\[CrossRef\]](#) [\[PubMed\]](#)
106. Kim, J.H.; Park, Y.B.; Ha, C.W.; Roh, Y.J.; Park, J.G. Adverse Reactions and Clinical Outcomes for Leukocyte-Poor Versus Leukocyte-Rich Platelet-Rich Plasma in Knee Osteoarthritis: A Systematic Review and Meta-analysis. *Orthop. J. Sports Med.* **2021**, *9*, 23259671211011948. [\[CrossRef\]](#) [\[PubMed\]](#)
107. Kuffler, D.P. Variables affecting the potential efficacy of PRP in providing chronic pain relief. *J. Pain Res.* **2019**, *12*, 109–116. [\[CrossRef\]](#)
108. Imam, S.S.; Al-Abbasi, F.A.; Hosawi, S.; Afzal, M.; Nadeem, M.S.; Ghoneim, M.M.; Alshehri, S.; Alzarea, S.I.; Alquraini, A.; Gupta, G.; et al. Role of platelet-rich plasma mediated repair and regeneration of cell in early stage of cardiac injury. *Regen. Ther.* **2022**, *19*, 144–153. [\[CrossRef\]](#) [\[PubMed\]](#)
109. Crowley, J.L.; Soti, V. Platelet-Rich Plasma Therapy: An Effective Approach for Managing Knee Osteoarthritis. *Cureus* **2023**, *15*, e50774. [\[CrossRef\]](#) [\[PubMed\]](#)
110. Xiong, Y.; Gong, C.; Peng, X.; Liu, X.; Su, X.; Tao, X.; Li, Y.; Wen, Y.; Li, W. Efficacy and safety of platelet-rich plasma injections for the treatment of osteoarthritis: A systematic review and meta-analysis of randomized controlled trials. *Front. Med.* **2023**, *10*, 1204144. [\[CrossRef\]](#)
111. Rezuş, E.; Burlui, A.; Cardoneanu, A.; Macovei, L.A.; Tamba, B.I.; Rezuş, C. From Pathogenesis to Therapy in Knee Osteoarthritis: Bench-to-Bedside. *Int. J. Mol. Sci.* **2021**, *22*, 2697. [\[CrossRef\]](#)
112. Paganelli, A.; Contu, L.; Condorelli, A.; Ficarelli, E.; Motolese, A.; Paganelli, R.; Motolese, A. Platelet-Rich Plasma (PRP) and Adipose-Derived Stem Cell (ADSC) Therapy in the Treatment of Genital Lichen Sclerosus: A Comprehensive Review. *Int. J. Mol. Sci.* **2023**, *24*, 6107. [\[CrossRef\]](#)
113. Ben-Nafa, W.; Munro, W. The effect of corticosteroid versus platelet-rich plasma injection therapies for the management of lateral epicondylitis: A systematic review. *Sicot J.* **2018**, *4*, 11. [\[CrossRef\]](#)
114. Lippi, L.; Ferrillo, M.; Turco, A.; Folli, A.; Moalli, S.; Refati, F.; Perrero, L.; Ammendolia, A.; de Sire, A.; Invernizzi, M. Multidisciplinary Rehabilitation after Hyaluronic Acid Injections for Elderly with Knee, Hip, Shoulder, and Temporomandibular Joint Osteoarthritis. *Medicina* **2023**, *59*, 2047. [\[CrossRef\]](#) [\[PubMed\]](#)
115. Encinas-Ullán, C.A.; Rodríguez-Merchán, E.C. Arthroscopic treatment of total knee arthroplasty complications. *EFORT Open Rev.* **2019**, *4*, 33–43. [\[CrossRef\]](#) [\[PubMed\]](#)

116. Samuelson, E.M.; Ebel, J.A.; Reynolds, S.B.; Arnold, R.M.; Brown, D.E. The Cost-Effectiveness of Platelet-Rich Plasma Compared With Hyaluronic Acid Injections for the Treatment of Knee Osteoarthritis. *Arthroscopy* **2020**, *36*, 3072–3078. [[CrossRef](#)]
117. Malahias, M.A.; Roumeliotis, L.; Nikolaou, V.S.; Chronopoulos, E.; Sourlas, I.; Babis, G.C. Platelet-Rich Plasma versus Corticosteroid Intra-Articular Injections for the Treatment of Trapeziometacarpal Arthritis: A Prospective Randomized Controlled Clinical Trial. *Cartilage* **2021**, *12*, 51–61. [[CrossRef](#)] [[PubMed](#)]
118. Rhon, D.I.; Kim, M.; Asche, C.V.; Allison, S.C.; Allen, C.S.; Deyle, G.D. Cost-effectiveness of Physical Therapy vs Intra-articular Glucocorticoid Injection for Knee Osteoarthritis: A Secondary Analysis From a Randomized Clinical Trial. *JAMA Netw. Open* **2022**, *5*, e2142709. [[CrossRef](#)] [[PubMed](#)]
119. Prinja, S.; Nandi, A.; Horton, S.; Levin, C.; Laxminarayan, R. Costs, effectiveness, and cost-effectiveness of selected surgical procedures and platforms. In *Disease Control Priorities: Essential Surgery*, 3rd ed.; World Bank Publications: Chicago, IL, USA, 2015; Volume 1, pp. 317–338.

**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.