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Review Article

Platelet-Rich Plasma and Low-Molecular-Weight Collagen Peptides in Regenerative Joint Therapy: Mechanistic Insights, Current Evidence and Future Directions: A Narrative Review

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Abstract

Platelet-Rich Plasma (PRP) has emerged as a promising regenerative therapy for osteoarthritis and joint disorders, yet its clinical efficacy is constrained by rapid platelet activation and transient growth factor release. Low-molecular-Weight collagen Peptides (LWPs) represent a novel biological modulator capable of influencing platelet behavior through direct interaction with glycoprotein VI (GPVI) signaling pathways. This systematic review synthesizes current evidence on the biochemical mechanisms underlying PRP-LWP interactions, with emphasis on GPVI-mediated platelet activation, growth factor release kinetics and therapeutic outcomes in joint applications. The canonical GPVI signaling cascade-involving Syk, PLCγ2 and Ca^{2+} mobilization-can be modulated by small peptides and competitive inhibitors, suggesting mechanistic plausibility for LWP-mediated regulation. While PRP demonstrates time-dependent growth factor release profiles that can be extended through fibrin-based delivery systems and LWPs exhibit chondroprotective and anti-inflammatory effects in preclinical models, direct experimental evidence for LWP-PRP synergy remains limited. Clinical studies demonstrate symptomatic improvement with PRP in early-to-moderate knee osteoarthritis, but formulation heterogeneity and the absence of LWP combination trials constrain definitive conclusions. This review identifies critical knowledge gaps and proposes future research directions for optimizing PRP-LWP formulations in regenerative orthopedics.

Keywords: Platelet-Rich Plasma; Collagen Peptides; GPVI Signaling; Osteoarthritis; Growth Factor Release; Cartilage Regeneration

Abbreviations

ACL: Anterior Cruciate Ligament; ADAMTS: A Disintegrin And Metalloproteinase with Thrombospondin Motifs; ACAN: Aggrecan; Akt: Protein Kinase B; BMP: Bone Morphogenetic Protein; Btk: Bruton's Tyrosine Kinase; Ca^{2+}: Calcium Ion; CEACAM1: Carcinoembryonic Antigen-Related Cell Adhesion Molecule 1; COX-2: Cyclooxygenase-2; COL2A1: Type II Collagen Gene; CRP: Collagen-Related Peptide; DAG: Diacylglycerol; ECM: Extracellular Matrix; FcRγ: Fc Receptor Gamma Chain; GFOGER: Glycine-Phenylalanine-Hydroxyproline-Glycine-Glutamate-Arginine (collagen-mimetic motif); GPVI: Glycoprotein VI; GSK3β: Glycogen Synthase Kinase 3 Beta; GPO: Glycine-Proline-Hydroxyproline motif; IKDC: International Knee Documentation Committee score; IGF-1: Insulin-like Growth Factor 1; IL-1β: Interleukin-1 Beta; IP3: Inositol 1,4,5-Trisphosphate; ITAM: Immunoreceptor Tyrosine-based Activation Motif; ITIM: Immunoreceptor Tyrosine-based Inhibitory Motif; JAK2: Janus Kinase 2; KOOS: Knee Injury and Osteoarthritis Outcome Score; L-PRP: Leukocyte-rich Platelet-Rich Plasma; LAT: Linker for Activation of T cells; LWP: Low-Molecular-Weight Collagen Peptides; MMP: Matrix Metalloproteinase; MSC: Mesenchymal Stem Cell; OA: Osteoarthritis; Orai1: Calcium Release-Activated Calcium Channel Protein 1; PDGF: Platelet-Derived Growth Factor; PEODA: Polyethylene Oxide Diacrylate; PLCγ2: Phospholipase C Gamma 2;

PIP2: Phosphatidylinositol 4,5-Bisphosphate; P-PRP: Pure Platelet-Rich Plasma; PRF: Platelet-Rich Fibrin; PRP: Platelet-Rich Plasma; QLSN: CEACAM1-derived peptide sequence; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; SH2: Src Homology 2 Domain; SLP-76: SH2 Domain-Containing Leukocyte Protein of 76 kDa; SOX9: SRY-Box Transcription Factor 9; SOCE: Store-Operated Calcium Entry; STAT5: Signal Transducer and Activator of Transcription 5; Syk: Spleen Tyrosine Kinase; TGF-β: Transforming Growth Factor Beta; VEGF: Vascular Endothelial Growth Factor

Introduction

Osteoarthritis (OA) is the most prevalent musculoskeletal disorder worldwide, affecting over 500 million individuals and representing a leading cause of chronic pain, functional disability and healthcare costs [1]. The pathophysiology of OA involves progressive degradation of articular cartilage, synovial inflammation, subchondral bone remodeling and periarticular soft tissue changes, culminating in joint failure. Current therapeutic strategies remain predominantly symptomatic, with limited disease-modifying interventions available for early-to-moderate disease stages [2]. Platelet-Rich Plasma (PRP) has emerged as a promising autologous biological therapy, leveraging supraphysiological concentrations of platelets to deliver growth factors including Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor-β (TGF-β), Vascular Endothelial Growth Factor (VEGF) and Insulin-Like Growth Factor-1 (IGF-1) directly to damaged tissues [3,4].

The therapeutic rationale for PRP in joint disorders centers on its capacity to modulate the intra-articular microenvironment through multiple mechanisms: stimulation of chondrocyte anabolic activity, enhancement of extracellular matrix synthesis, recruitment and differentiation of Mesenchymal Stem Cells (MSCs) and attenuation of inflammatory cytokine expression [5,6]. Clinical evidence demonstrates symptomatic improvement and functional gains in patients with early-stage knee OA following intra-articular PRP injection, with some studies reporting sustained benefits extending to 36 months [7-9].

Despite these promising outcomes, PRP therapy faces significant limitations that constrain its clinical efficacy. Platelet activation in conventional PRP formulations occurs rapidly upon exposure to endogenous collagen and thrombin within the joint space, resulting in a "burst release" pattern characterized by maximal growth factor secretion within the first few hours followed by rapid decline [10,11]. This transient bioavailability profile may be insufficient to sustain the prolonged cellular responses required for cartilage regeneration and tissue remodeling. Additionally, substantial heterogeneity in PRP preparation protocols including variations in platelet concentration, leukocyte content and activation methods-contributes to inconsistent clinical outcomes and challenges in standardization [12].

Low-molecular-Weight collagen Peptides (LWPs), typically ranging from 0.5 to 10 kDa and derived from enzymatic hydrolysis of native collagen, have attracted increasing attention as bioactive molecules with potential chondroprotective and regenerative properties [13,14]. Preclinical studies demonstrate that oral or local administration of LWPs can reduce cartilage degradation, enhance type II collagen synthesis, suppress inflammatory mediator expression and promote chondrocyte proliferation in animal models of OA [15,16]. The molecular mechanisms underlying these effects remain incompletely characterized but appear to involve modulation of growth factor signaling pathways, including upregulation of IGF-1 and Bone Morphogenetic Proteins (BMPs), as well as direct effects on extracellular matrix metabolism [17].

A particularly intriguing aspect of LWP biology is their potential to interact with platelet surface receptors specifically Glycoprotein VI (GPVI), the primary collagen receptor responsible for platelet activation and aggregation [18]. GPVI engagement by native collagen triggers a well-characterized signaling cascade involving immunoreceptor tyrosine-based activation motif (ITAM) phosphorylation, recruitment and activation of Spleen tyrosine kinase (Syk), Phospholipase Cγ2 (PLCγ2) activation and subsequent intracellular calcium mobilization culminating in platelet degranulation and integrin αIIbβ3 activation [19,20]. Small peptides and molecules capable of binding GPVI have been shown to modulate this signaling pathway, acting either as competitive inhibitors that attenuate excessive platelet activation or as partial agonists that induce controlled, low-level activation [21,22].

The hypothesis that LWPs may function as GPVI modulators in PRP formulations presents a compelling theoretical framework for optimizing growth factor release kinetics and therapeutic outcomes. By competitively binding to GPVI, LWPs could potentially attenuate the rapid, high-intensity platelet activation characteristic of conventional PRP, instead promoting a more gradual and sustained degranulation profile. Simultaneously, as partial agonists, LWPs might induce low-level platelet

activation sufficient to maintain continuous growth factor secretion over extended periods. Furthermore, LWPs could serve as extracellular matrix mimetics within the fibrin scaffold formed during PRP activation, enhancing growth factor retention and prolonging intra-articular bioavailability [23].

Despite the mechanistic plausibility of LWP-PRP synergy, direct experimental evidence supporting this hypothesis remains limited. No published studies have systematically investigated the effects of LWP supplementation on PRP platelet activation kinetics, growth factor release profiles or combined therapeutic efficacy in joint applications. This knowledge gap represents a critical barrier to the rational design of optimized PRP-LWP formulations for clinical translation.

Aims of This Review

The present systematic review aims to synthesize current evidence on the biochemical interactions between LWPs and PRP, with particular focus on: (1) the molecular mechanisms of GPVI-mediated platelet activation and its modulation by peptides and small molecules; (2) PRP growth factor release kinetics and strategies for sustained delivery; (3) the biological effects of LWPs on chondrocytes, MSCs and joint tissues (4); and clinical outcomes of PRP therapy in osteoarthritis. By integrating these distinct lines of evidence, we seek to establish a mechanistic foundation for future investigations of LWP-PRP combination therapy and identify critical research priorities for advancing this therapeutic approach.

Methodology

A literature review was conducted to identify studies published between 2016 and 2026 related to PRP, GPVI signaling, collagen peptides, cartilage regeneration and growth factor delivery systems. Peer-reviewed articles involving PRP biology, platelet activation, collagen-mediated signaling, chondrogenesis and osteoarthritis outcomes were included, while conference abstracts and low-quality studies were excluded.

Eligible studies included original research articles, systematic reviews and clinical trials evaluating PRP mechanisms, collagen peptide biology, platelet receptor signaling and joint therapy outcomes. Data extraction focused on GPVI signaling pathways, modulation of platelet function, PRP growth factor release kinetics, biological effects of Low-molecular-Weight Peptides (LWPs) on cartilage and chondrocytes and clinical outcomes in osteoarthritis. Due to study heterogeneity, findings were synthesized using a narrative thematic review approach.

Results

GPVI Signaling Mechanisms in Platelet Activation

Glycoprotein VI (GPVI) represents the primary collagen receptor on platelet surfaces and serves as a critical mediator of platelet activation in response to vascular injury and extracellular matrix exposure [24]. The molecular architecture of GPVI signaling has been extensively characterized through biochemical, genetic and pharmacological studies, revealing a canonical ITAM-dependent pathway that couples collagen binding to intracellular calcium mobilization and platelet functional responses [25].

GPVI exists as a dimer on the platelet surface, associated with the Fc receptor γ-chain (FcRγ) that contains the ITAM motif essential for signal transduction [26]. Upon collagen binding, GPVI dimers undergo clustering, which initiates the signaling cascade [27]. This clustering event triggers phosphorylation of tyrosine residues within the ITAM sequence of FcRγ by Src family kinases, particularly Fyn and Lyn [28]. The phosphorylated ITAM serves as a docking site for the tandem SH2 domains of Syk, leading to Syk recruitment, autophosphorylation and activation [29].

Activated Syk phosphorylates multiple downstream substrates, most notably the adaptor protein Linker for Activation of T cells (LAT), which nucleates the formation of a signalosome complex including SLP-76, Gads and PLCγ2 [30]. Phosphorylation of PLCγ2 by Syk and Bruton's tyrosine kinase (Btk) activates its enzymatic activity, catalyzing hydrolysis of Phosphatidylinositol 4,5-bisphosphate (PIP2) to generate Inositol 1,4,5-trisphosphate (IP3) and Diacylglycerol (DAG) (31). IP3 binds IP3 receptors on the dense tubular system, triggering release of Ca^{2+} from intracellular stores and subsequent Store-Operated Calcium Entry (SOCE) through Orai1 channels [32]. The resulting elevation in cytosolic Ca^{2+} concentration activates multiple effector pathways, including Protein Kinase C (PKC) isoforms, calpain and myosin light chain kinase, culminating in platelet shape change, granule secretion and integrin αIIbβ3 activation [33].

Experimental evidence from multiple studies confirms the essential role of each component in this signaling cascade. Genetic deletion or pharmacological inhibition of Syk abolishes collagen-induced platelet aggregation and thrombus formation on collagen surfaces [34]. Similarly, PLCγ2-deficient platelets exhibit severely impaired calcium mobilization and functional responses to GPVI agonists [35]. The tetraspanin Tspan18 has been identified as a regulator of Orai1-mediated calcium entry, with Tspan18-deficient platelets showing reduced GPVI-mediated aggregation and spreading, particularly at intermediate agonist concentrations [36].

The GPVI signaling pathway is subject to multiple levels of regulation. Negative regulatory mechanisms include ITIM-containing receptors such as PECAM-1, CEACAM1 and G6b-B, which recruit phosphatases that dephosphorylate Syk and other signaling intermediates [37]. Post-translational modifications, including ubiquitylation of Syk and PLCγ2, also modulate signaling intensity and duration [38]. Additionally, the spatial organization of GPVI signaling is influenced by membrane microdomains, with evidence suggesting functional cooperation between GPVI and other receptors within lipid rafts (Fig. 1) [39].

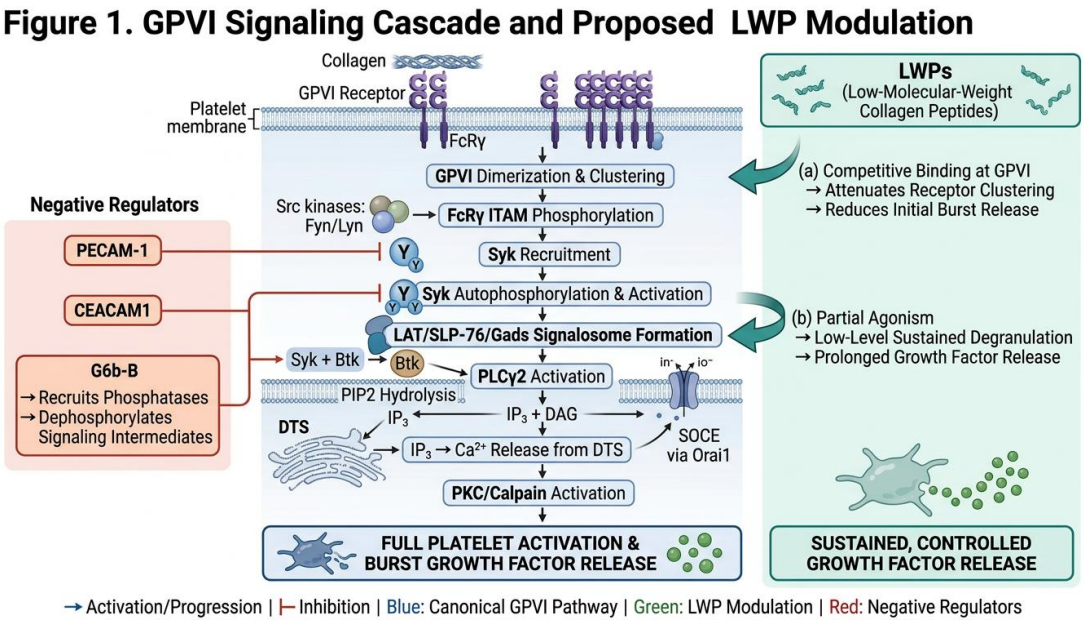

Figure 1: GPVI signaling cascade and proposed LWP modulation.

The canonical GPVI signaling pathway (blue) proceeds from collagen binding and GPVI dimerization/clustering, through FcRγ ITAM phosphorylation (Fyn/Lyn), Syk recruitment and autophosphorylation, LAT/SLP-76/Gads signalosome formation, PLCγ2 activation, PIP2 hydrolysis to IP3 + DAG, Ca^{2+} release from the Dense Tubular System (DTS) and store-operated calcium entry (SOCE) via Orai1 and PKC/calpain activation, culminating in full platelet activation and burst growth factor release. LWP modulation (green) acts at two levels: (a) competitive binding at GPVI attenuates receptor clustering and reduces initial burst release; (b) partial agonism at the signalosome level sustains low-level degranulation, yielding prolonged, controlled growth factor release. Negative regulators (red) PECAM-1, CEACAM1 and G6b-B inhibit Syk and downstream intermediates via phosphatase recruitment. DTS, dense tubular system; SOCE, store-operated calcium entry.

The specificity of GPVI for collagen is determined by recognition of the Glycine-proline-hydroxyproline (GPO) triplet repeat motif characteristic of collagen triple helices [40]. Synthetic Collagen-Related Peptides (CRPs) containing (GPO)n sequences serve as selective GPVI agonists and have been instrumental in dissecting GPVI-specific signaling from integrin $\alpha 2\beta 1$-mediated adhesion [41]. Only collagen peptides with the (GPO)n sequence and fibril-type collagen evoke Syk-dependent Ca^{2+} rises in platelet suspensions, confirming the structural requirements for GPVI engagement [42].

Modulation of GPVI Signaling by Peptides and Small Molecules

The therapeutic potential of targeting GPVI signaling has motivated extensive investigation of molecules capable of modulating this pathway. Multiple classes of GPVI modulators have been identified, including competitive inhibitors, antibodies and peptide-based antagonists, each demonstrating distinct mechanisms of action and functional consequences [43]. Artesunate, an antimalarial drug, has been shown to directly bind recombinant human GPVI with high affinity (K_D = 44 nM) and inhibit

collagen-induced platelet aggregation [44]. Mechanistic studies demonstrate that artesunate reduces collagen-stimulated granule release, calcium mobilization and GPIIb/IIIa activation, while blocking phosphorylation of Syk, PLCγ2, PKC, Akt and MAPKs. These findings indicate that artesunate acts as a competitive inhibitor of collagen-GPVI binding, thereby preventing initiation of the entire signaling cascade. Importantly, artesunate exhibits antithrombotic effects *in-vivo* with minimal bleeding risk, suggesting that GPVI inhibition may provide a favorable therapeutic window compared to conventional antiplatelet agents [44]. Peptide-based GPVI modulators have also been developed and characterized. A CEACAM1-derived peptide (QLSN) attenuates collagen-induced aggregation and reduces convulxin-mediated phosphorylation of Src, Akt, Syk and PLCγ2 in human platelets. The QLSN peptide significantly attenuated collagen-induced platelet aggregation at concentrations of 25 μM and 50 μM, indicating inhibition of GPVI signaling at the level of early tyrosine phosphorylation events [45]. This peptide appears to interfere with GPVI clustering and early signaling complex formation, thereby dampening downstream activation.

Antibody-based approaches have demonstrated that blocking GPVI clustering prevents downstream signaling and functional responses. An anti-GPVI nanobody blocked collagen- and plaque-induced GPVI clustering, signaling and thrombus formation, illustrating that interruption of GPVI clustering/engagement prevents downstream Syk-PLCγ2 activation and functional aggregation [46]. Similarly, the humanized Fab fragment ACT017 inhibits collagen-induced aggregation with an IC50 of 3.2 ± 2.5 μg/mL by blocking collagen interaction with GPVI [47].

Natural compounds have also been investigated as GPVI modulators. Fruitflow, a tomato-derived extract, inhibits platelet function by suppressing Akt/GSK3β, Syk/PLCγ2 and p38 MAPK phosphorylation in collagen-stimulated platelets [48]. This multi-target inhibition profile suggests that certain bioactive compounds can modulate GPVI signaling at multiple nodes, potentially offering more comprehensive regulation of platelet activation.

The concept of partial agonism at GPVI is supported by observations that the intensity of GPVI signaling can be modulated by varying agonist concentration, receptor clustering density and co-receptor engagement [49]. Theoretical models predict that low-level GPVI activation, insufficient to trigger full aggregation, could nonetheless induce controlled degranulation and growth factor release [50]. This principle has been exploited in the development of GPVI-Fc fusion proteins such as Revacept, which competitively inhibit collagen binding while potentially inducing low-level signaling through receptor crosslinking [51].

Importantly, the structural requirements for GPVI engagement suggest that collagen-derived peptides could theoretically interact with this receptor. However, the available literature does not provide direct experimental evidence that Low-molecular-Weight collagen Peptides (LWPs) act as GPVI partial agonists or competitive inhibitors in platelets. While collagen and collagen-derived peptides interact with multiple cell receptors and modulate signaling in diverse cell types, specific platelet-GPVI functional studies with dietary or bioactive collagen peptides have not been reported in the current evidence base. This represents a critical knowledge gap that must be addressed through targeted experimental investigation [52].

PRP Growth Factor Release Kinetics and Delivery Systems

The therapeutic efficacy of PRP is fundamentally dependent on the temporal profile of growth factor release and the duration of bioavailability within the target tissue. Characterization of PRP release kinetics has revealed substantial heterogeneity based on preparation method, activation protocol and delivery system, with important implications for clinical outcomes [53].

Time-course analysis of Pure-PRP (P-PRP) and Leukocyte-rich PRP (L-PRP) demonstrated distinct temporal patterns for multiple soluble mediators over 168 hours . Some molecules peaked within approximately 18 hours and subsequently declined; others progressively increased to 168 hours; and others peaked at intermediate time points. L-PRP and P-PRP differed in their support of synovial fibroblast growth and hyaluronic acid production *in-vitro*, demonstrating preparation- and time-dependent functional release profiles [54]. This temporal heterogeneity suggests that different growth factors and cytokines are released through distinct mechanisms, with some representing immediate platelet degranulation products and others reflecting ongoing cellular synthesis or matrix-bound factor liberation.

The rapid release kinetics of conventional PRP formulations have motivated development of delivery systems designed to prolong growth factor bioavailability. Embedding platelet concentrates into interpenetrating hydrogel/fibrin networks greatly increased gel stability and produced sustained, controllable release of PDGF and TGF-β1, while improving adhesiveness .

Interpenetrating Polymer Networks (IPNs) demonstrated the highest stability and sustained release of PDGF and TGF-β1 over prolonged periods, with release kinetics being mainly diffusional or first-order. In contrast, PRP gels without hydrogel reinforcement showed significant burst release, with 60-70% of TGF-β1 and PDGF released within 100 hours [55].

Alternative delivery strategies have explored incorporation of PRP into various biomaterial scaffolds. Injectable fucoidan and biological macromolecule hybrid hydrogels enabled slower, more sustained release of PDGF compared to traditional PRP gelb. Fucoidan, a heparinoid compound, binds heparin-binding growth factors to control their release rate, with cumulative PDGF release reaching approximately 200 pg/mL by day 16 [56]. Similarly, silk fibroin-PRP injectable hydrogels have been developed for controlled-release of growth factors in knee osteoarthritis applications [57].

Exosome-based delivery represents an emerging approach to prolonging PRP bioactivity. PRP-derived exosomes incorporated into a thermosensitive hydrogel composed of a Poloxamer-407 and 188 mixture allowed for continuous exosome release for 28 days, increasing local retention and therapeutic efficacy in subtalar osteoarthritis [58]. This approach leverages the stability and biological activity of exosomal cargo while utilizing the hydrogel as a sustained-release depot.

Microsphere encapsulation offers another strategy for controlled PRP factor delivery. Super-activated Platelet Lysate (sPL) encapsulated in PLGA/chitosan/gelatin nanospheres demonstrated rapid growth factor release within the first 72 hours, followed by stabilization, with different formulations releasing factors at varying rates over 10 days [59]. This biphasic release profile combining initial burst release to stimulate acute cellular responses with sustained low-level release to maintain chronic signaling may be optimal for tissue regeneration applications.

Rationale for Sustained Release in Clinical Outcomes

The clinical relevance of sustained growth factor release is underscored by evidence linking fibrin-rich PRP formulations to improved long-term outcomes. Co-administration of PRP with injectable PRF (a fibrin-rich fraction) was associated with prolonged inter-injection intervals and an 80.18% 36-month "survival" (no surgery requirement) in a large cohort of knee OA patients . This finding supports the premise that extending growth factor bioavailability through optimized delivery systems translates into longer clinical effect windows, although mechanistic release data for the combination were not reported [60].

The fibrin architecture formed during PRP activation plays a critical role in determining short-term versus sustained protein release and bioavailability. However, formulation heterogeneity remains a major source of variability across studies, complicating efforts to establish standardized protocols. Foundational descriptions of PRP fibrin matrices emphasize that fibrin network density, fiber diameter and crosslinking degree all influence growth factor retention and release kinetics [61].

Quantitative characterization of growth factor concentrations in PRP preparations reveals substantial variability. One study reported initial growth factor levels in activated PRP as: VEGF (312 ± 123.2 ng/mL), PDGF (279 ± 152 ng/mL) and TGF-β1 (2.0 ± 0.1 ng/mL) [62]. Another study found PDGF-BB concentration in PRP releasate to be 1.2×10^5 pg/mL [63]. In equine synovial fluid following PRP injection, PDGF-BB concentrations remained unchanged on Day 7 compared to Day 1, while TGF-β1 decreased, with synovial fluid TGF-β1 concentration rapidly induced with a maximum within one hour and PDGF-BB release constant and sustained over days [64].

Importantly, the available literature does not report studies directly testing PRP combined with Low-molecular-Weight collagen Peptides (LWPs) for release kinetics or clinical outcomes. This absence of direct evidence represents a significant gap in the knowledge base and underscores the need for systematic investigation of PRP-LWP formulations.

Biological Effects of Low-Molecular-Weight Collagen Peptides

Low-molecular-Weight collagen Peptides (LWPs) have demonstrated diverse biological activities relevant to cartilage health and joint function in preclinical models. These effects encompass chondroprotection, anabolic stimulation, anti-inflammatory activity and modulation of mesenchymal stem cell differentiation [65].

In an Anterior Cruciate Ligament (ACL) transection rabbit OA model, oral administration of Low-Molecular-Weight Collagen Peptide (LMCP) reduced cartilage damage and proteoglycan loss while promoting extracellular matrix synthesis by patient-

derived chondrocytes *in-vitro* in a dose-dependent manner [66]. This chondroprotective effect suggests that LWPs can attenuate cartilage degradation processes while simultaneously enhancing anabolic activity.

Marine-derived collagen peptides have shown particularly robust biological activity. Atlantic salmon bone collagen peptides increased type II collagen expression, reduced type X collagen and chondrocyte apoptosis, downregulated Matrix Metalloproteinases (MMPs) and ADAMTS expression and decreased IL-1β, TNF-α and IL-6 in cell and rat OA models [67]. *In-vivo*, these peptides improved pain tolerance and cartilage biomarkers. Similarly, jellyfish collagen peptide (5 mg/kg body weight) demonstrated significant potential for both cartilage protection and regeneration in an ACLT medial meniscectomy rat model, inhibiting proinflammatory cytokines (COX-2, MMP-13, CTX-II) and promoting type II collagen synthesis [68].

The molecular mechanisms underlying LWP biological activity involve modulation of growth factor signaling pathways. A fish-derived hydrolyzed collagen tripeptide (CTP20, <500 Da, containing >3.2% Gly-Pro-Hyp) enhanced proliferation (28.2%), alkaline phosphatase activity (32.0%), collagen synthesis (1.14-fold) and calcium deposition (1.15-fold) in SW1353 chondrocytes [69]. CTP20 increased IGF-1 and BMP expression and activated JAK2/STAT5 signaling in chondrocytes and growth plates, indicating promotion of endochondral ossification [69]. This upregulation of anabolic growth factors represents a potential mechanism for synergy with PRP-derived factors.

Collagen Mimetic Peptides (CMPs) combined with Polyethylene Oxide Diacrylate (PEODA) activated ECM component synthesis (glycosaminoglycans and collagen) in MSCs, while MSCs cultured with CMP/PEODA showed lower type X collagen expression, a hypertrophy marker. The GFOGER peptide, a collagen triple helix mimetic, increased MSC proliferative activity and stimulated type II collagen synthesis [70]. These findings suggest that specific collagen-derived sequences can direct MSC differentiation toward a chondrogenic phenotype while suppressing hypertrophic differentiation.

Immunomodulatory effects of collagen peptides have also been documented. Squid type II collagen mediated cartilage repair in degenerative OA by immunomodulating M2 macrophages, inhibiting apoptosis and suppressing chondrocyte hypertrophy in an *in-vivo* model. This collagen induced M2 macrophage polarization and increased TGF-β and IGF levels, promoting a pro-chondrogenic environment [71]. The ability of collagen peptides to modulate the inflammatory microenvironment represents an additional mechanism by which they could complement PRP therapy.

Translational evidence for LWP benefit in human OA has begun to accumulate from randomized controlled trials. In a double-blind, placebo-controlled trial, patients with Kellgren-Lawrence grade I or II knee osteoarthritis who received daily supplementation of 3,000 mg low-molecular-weight collagen peptides over 180 days demonstrated a statistically significant reduction in WOMAC pain subscores (−1.90 ± 4.14 vs. 0.61 ± 3.97; $p = 0.006$), alongside improvements in physical function and total WOMAC scores [72]. Notably, no significant between-group differences were detected in joint space width or systemic inflammatory markers, which implies that the observed clinical benefit operates primarily through symptom-modulating pathways rather than through measurable structural joint modification at this time point [72]. Complementary evidence from a separate randomized trial demonstrated that daily oral intake of type I collagen-derived bioactive peptides with a mean molecular weight of 3 kDa produced a statistically significant attenuation of exercise-induced knee pain (−21.9 ± 18.3 mm) relative to placebo (−15.6 ± 18.5 mm) in young physically active adults, extending the evidence base beyond an OA population to mechanically loaded joints [73].

Taken together, these findings establish clinical proof-of-concept for LWP-mediated joint symptom relief. However, no published study has directly evaluated PRP and LWP in combination, nor has synergistic enhancement of mesenchymal stem cell chondrogenesis beyond the additive effects of each agent individually been demonstrated. Closing this evidence gap is a prerequisite for advancing PRP-LWP combination therapy toward clinical translation.

Clinical Outcomes of PRP in Osteoarthritis

Intra-articular PRP injection for knee osteoarthritis has been evaluated in multiple clinical studies demonstrating consistent symptomatic and functional improvements. While heterogeneity in PRP preparation, patient selection and outcome measures complicates direct comparison across trials, several robust patterns have emerged from the evidence base [74].

A randomized controlled trial comparing PRP versus autologous adipose tissue injections in 40 OA patients (with 20 healthy controls) found comparable improvements in VAS, KOOS, WOMAC and IKDC scores at serial assessments, with PRP showing distinct gene expression features in the platelet product [75]. This study suggests that PRP efficacy is comparable to other autologous biological therapies, although the mechanisms of action may differ. A prospective series of 98 patients receiving two standardized autologous PRP injections 3 weeks apart demonstrated significant VAS and WOMAC improvement at 6 weeks, 3 months and 6 months, with partial waning of effect by 12 months [76]. This temporal pattern of benefit-with maximal improvement in the first months followed by gradual decline is consistent across multiple studies and suggests that repeat injections may be necessary to maintain clinical benefit.

Long-term outcomes data provide important insights into the durability of PRP therapy. A prospective cohort of 368 patients receiving a single 4 mL PRP + 4 mL injectable PRF injection demonstrated a 36-month surgical-free survival of 80.18%, with a mean of 2.52 injections and increasing intervals between injections over time [77]. This suggests that the combination of PRP with fibrin-rich PRF may extend the duration of clinical benefit, potentially through sustained growth factor release mechanisms.

Additional prospective studies have confirmed symptomatic benefit. A study of 100 knees in 75 patients receiving pure PRP injections reported patient satisfaction, pain reduction and range of motion improvement at 9 months in the majority of patients, with no major complications [78]. Another prospective study of 60 patients with primary knee OA grade 1-2 found that VAS decreased from a mean of 6.45 to 3.76 at 6 months, with significant WOMAC improvement (79).

Study	Design	n	PRP Type	Follow-up	Primary Outcome	Key Finding
Kaszynski, et al., [75]	RCT	40	Autologous PRP	12 months	VAS, KOOS, WOMAC, IKDC	PRP comparable to adipose tissue injections
Rai, et al., [76]	Prospective series	98	Standardized autologous PRP	12 months	VAS, WOMAC	Significant improvement at 6 weeks-6 months; waning at 12 months
Cheeva-akrapan and Turajane [77]	Prospective cohort	368	PRP + injectable PRF	36 months	Surgical-free survival	80.18% survival; mean 2.52 injections
Nair, et al., [78]	Prospective	75 (100 knees)	Pure PRP	9 months	Pain, ROM, satisfaction	Improvement in majority; no major complications
Sharma, et al., [79]	Prospective	60	PRP	6 months	VAS, WOMAC	VAS reduced from 6.45 to 3.76

Table 1: Summary of key clinical studies of intra-articular PRP in knee osteoarthritis.

The clinical evidence base demonstrates several consistent patterns:

1. PRP provides symptomatic relief and functional improvement in early-to-moderate knee OA
2. Maximal benefit typically occurs within the first 3-6 months post-injection
3. Effect magnitude gradually diminishes over 12 months
4. Repeat injections can extend clinical benefit
5. Serious adverse events are rare. However, substantial heterogeneity in PRP products including variations in platelet concentration (ranging from 1.6- to 5-fold over baseline), leukocyte content (pure-PRP vs. leukocyte-rich PRP) and activation methods complicates efforts to establish optimal protocols [80].

Importantly, no clinical trials of PRP combined with LWPs were identified in the provided evidence base. This absence of clinical data represents a critical gap in the translational pathway for PRP-LWP combination therapy and underscores the need for well-designed clinical trials to test this approach (Fig. 2).

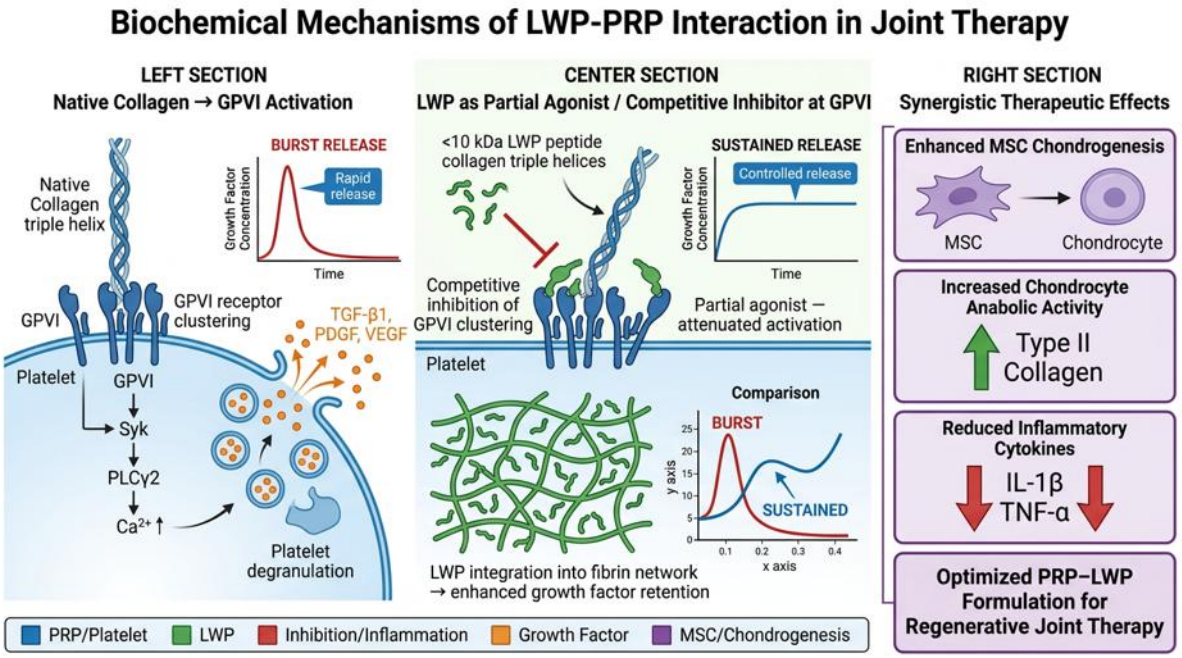

Figure 2: Biochemical mechanisms of LWP-PRP interaction in joint therapy. The diagram illustrates the proposed molecular mechanisms by which Low-molecular-Weight collagen Peptides (LWPs) modulate platelet-rich plasma (PRP) function. Native collagen induces full GPVI activation through receptor clustering, triggering the Syk-PLCγ2-Ca^{2+} signaling cascade that leads to rapid platelet degranulation and burst release of growth factors. LWPs are hypothesized to act as partial agonists and competitive inhibitors at GPVI, attenuating excessive activation while promoting sustained, controlled growth factor release. The resulting shift from burst to sustained release kinetics, combined with LWP integration into the fibrin network for enhanced growth factor retention, produces synergistic therapeutic effects including enhanced MSC chondrogenesis, increased chondrocyte anabolic activity and reduced inflammatory cytokine expression (IL-1β, TNF-α). This mechanistic framework provides a theoretical basis for optimizing PRP-LWP formulations in regenerative joint therapy.

Discussion

Mechanistic Integration: GPVI as a Therapeutic Target

The synthesis of evidence across GPVI signaling, platelet activation modulation and PRP release kinetics reveals a coherent mechanistic framework for understanding how low-molecular-weight collagen peptides could theoretically modulate PRP function. The canonical GPVI signaling pathway characterized by ITAM phosphorylation, Syk activation, PLCγ2-mediated calcium mobilization and subsequent platelet degranulation represents a druggable target with established precedent for pharmacological modulation [81].

The demonstration that small molecules (artesunate, K_D = 44 nM) and peptides (QLSN, effective at 25-50 μM) can competitively inhibit GPVI signaling establishes proof-of-concept that collagen-binding site occupancy can attenuate platelet activation [82,83]. The structural requirements for GPVI engagement-specifically recognition of GPO triplet repeats in collagen triple helices-suggest that collagen-derived peptides retaining these motifs could theoretically interact with GPVI [84]. However, the relationship between peptide molecular weight, sequence composition and GPVI binding affinity remains incompletely characterized.

The concept of partial agonism at GPVI is supported by observations that signaling intensity can be modulated by varying agonist concentration and receptor clustering density [85]. Low-level GPVI activation, insufficient to trigger full aggregation, could nonetheless induce controlled degranulation a phenomenon that could be exploited to achieve sustained growth factor release from PRP. This theoretical framework is consistent with the observation that different collagen preparations (fibrillar, soluble, native, denatured) elicit varying degrees of platelet activation [86].

The temporal dynamics of PRP growth factor are released characterized by rapid initial burst followed by decline align with the kinetics of GPVI-mediated platelet activation and degranulation. The demonstration that interpenetrating hydrogel networks can convert burst release to sustained release by physically constraining growth factor diffusion suggests that matrix-based strategies can effectively modulate bioavailability [87]. LWPs could theoretically contribute to this effect by serving as matrix components that enhance fibrin network density and growth factor retention through heparin-binding domain interactions.

Theoretical Framework for LWP-PRP Synergy

Integration of the evidence on GPVI modulation, PRP release kinetics and LWP biological effects supports a multi-level theoretical framework for PRP-LWP synergy:

Level 1: Direct GPVI modulation. LWPs containing GPO motifs could competitively bind GPVI, attenuating the rapid, high-intensity activation induced by endogenous collagen exposure in the joint space. This competitive inhibition would reduce the magnitude of initial burst release while potentially inducing low-level partial agonism sufficient to maintain continuous degranulation over extended periods. The net effect would be a shift from rapid, transient growth factor availability to sustained, prolonged release.

Level 2: Matrix-mediated growth factor retention. LWPs incorporated into the PRP fibrin network could enhance growth factor retention through multiple mechanisms:

1. Increasing fibrin network density and reducing pore size, thereby constraining diffusion
2. Providing additional heparin-binding sites for growth factors such as PDGF, TGF-β and VEGF
3. Serving as ECM mimetics that stabilize growth factor-receptor interactions. This matrix-mediated effect is supported by evidence that fucoidan and other heparin-binding molecules can prolong growth factor release from PRP formulations [88]

Level 3: Synergistic cellular effects. The combination of PRP-derived growth factors (PDGF, TGF-β, VEGF, IGF-1) with LWP-induced upregulation of endogenous growth factor expression (IGF-1, BMPs) could produce synergistic anabolic effects on chondrocytes and MSCs. LWPs have been shown to activate JAK2/STAT5 signaling and increase IGF-1 and BMP expression ,pathways that converge with PRP growth factor signaling to enhance chondrogenic differentiation and ECM synthesis [89]. Additionally, the anti-inflammatory effects of LWPs, including downregulation of IL-1β, TNF-α and MMPs, could complement PRP's immunomodulatory activity to create a more favorable microenvironment for cartilage regeneration [90].

Level 4: Temporal optimization of release kinetics. The ideal growth factor release profile for cartilage regeneration likely involves an initial moderate-intensity signal to recruit and activate resident cells, followed by sustained low-level signaling to maintain anabolic activity and suppress catabolic processes over weeks to months. LWP modulation of PRP activation could theoretically achieve this biphasic profile by attenuating initial burst release while prolonging the tail of sustained release.

Clinical Implications and Translational Potential

The clinical evidence for PRP in knee OA demonstrates consistent symptomatic benefit in early-to-moderate disease, with effect sizes comparable to or exceeding those of hyaluronic acid and corticosteroid injections [91]. However, the temporal pattern of benefit-with maximal improvement at 3-6 months followed by gradual decline suggests that current PRP formulations provide insufficient duration of biological activity to achieve sustained disease modification [92].

The theoretical framework for LWP-PRP synergy suggests several potential clinical advantages: (1) prolonged duration of symptomatic benefit through sustained growth factor release; (2) enhanced cartilage regeneration through synergistic anabolic effects; (3) improved anti-inflammatory activity through complementary mechanisms; and (4) potential for reduced injection frequency due to extended bioavailability. These potential benefits must be weighed against considerations of formulation complexity, regulatory requirements and cost-effectiveness. Translation of PRP-LWP combination therapy to clinical practice would require systematic investigation of several key parameters: optimal LWP molecular weight range and sequence composition; LWP:PRP ratio for maximal synergy; timing of LWP incorporation (pre-activation, during activation, post-activation); effects on PRP gelation kinetics and mechanical properties; and safety and immunogenicity of the combined formulation. Preclinical studies in relevant animal models (e.g., ACL transection, meniscectomy, spontaneous OA models) would be essential to establish proof-of-concept before advancing to human trials.

Limitations and Evidence Gaps

This systematic review identifies several critical limitations in the current evidence base that constrain definitive conclusions regarding LWP-PRP interactions:

Absence of direct experimental evidence. No published studies have directly tested the effects of LWPs on PRP platelet activation kinetics, GPVI signaling or growth factor release profiles. The theoretical framework presented here is based on extrapolation from separate lines of evidence-GPVI modulation by other peptides and the biological effects of LWPs in non-platelet systems. Direct biochemical and functional studies are urgently needed to validate or refute the hypothesis that LWPs act as GPVI modulators.

Heterogeneity in PRP preparation and characterization. The substantial variability in PRP preparation protocols, platelet concentrations, leukocyte content and activation methods across studies complicates efforts to establish standardized baseline parameters for comparison. This heterogeneity extends to growth factor quantification methods, with different studies using different assays and reporting different units, limiting quantitative synthesis.

Limited mechanistic characterization of LWP effects. While LWPs demonstrate chondroprotective and anti-inflammatory effects in preclinical models, the molecular mechanisms underlying these effects remain incompletely characterized. The specific receptors, signaling pathways and cellular targets mediating LWP biological activity require further investigation. Additionally, the relationship between LWP molecular weight, sequence composition and biological activity is not well defined, limiting rational design of optimized formulations.

Absence of clinical trials combining PRP and LWPs. The lack of clinical data on PRP-LWP combination therapy represents a critical gap in the translational pathway. While both PRP and LWPs individually demonstrate clinical benefit in OA, their combined effects, potential synergy and safety profile remain unknown.

Limited long-term outcome data. Most clinical studies of PRP in OA report outcomes at 6-12 months, with relatively few studies extending to 24-36 months. The long-term effects of PRP on cartilage structure, disease progression and need for surgical intervention require further investigation. Similarly, the durability of LWP effects and optimal dosing regimens for sustained benefit are not well established.

Future Research Directions

Based on the identified evidence gaps, several priority research directions emerge:

Direct investigation of LWP-GPVI interactions. *In-vitro* studies should systematically characterize the binding affinity, specificity and functional consequences of LWP interaction with GPVI. Surface plasmon resonance, isothermal titration calorimetry and immunoprecipitation studies could quantify binding parameters. Functional assays should assess effects on platelet aggregation, calcium mobilization, Syk/PLCγ2 phosphorylation and degranulation response to collagen and CRP stimulation. Structure-activity relationship studies should define the molecular weight range, sequence motifs and structural features required for GPVI modulation.

Characterization of LWP effects on PRP release kinetics. Time-course studies should quantify the effects of LWP supplementation on growth factor release from activated PRP over hours to weeks. Multiple PRP preparation methods (P-PRP, L-PRP) and LWP formulations should be tested. Growth factor quantification should include PDGF, TGF-β, VEGF, IGF-1 and other relevant mediators using standardized assays. Rheological characterization should assess effects on fibrin network properties, gelation kinetics and mechanical stability.

Preclinical efficacy studies in OA models. Well-controlled animal studies should compare PRP alone, LWPs alone and PRP-LWP combinations in established OA models (e.g., ACL transection, meniscectomy or spontaneous OA in guinea pigs or rats). Outcome measures should include histological assessment of cartilage structure, immunohistochemical analysis of matrix components (type II collagen, aggrecan, type X collagen), quantification of inflammatory markers and functional assessment of joint mechanics. Dose-response studies should identify optimal LWP:PRP ratios.

Mechanistic studies of cellular responses. *In-vitro* studies should characterize the effects of PRP-LWP combinations on primary human chondrocytes and MSCs, including proliferation, differentiation markers (SOX9, COL2A1, ACAN), matrix synthesis and inflammatory mediator expression. Signaling pathway analysis should identify points of convergence and synergy between PRP and LWP effects. Three-dimensional culture systems and tissue-engineered constructs should be used to model the intra-articular environment.

Clinical trials of PRP-LWP combination therapy. Phase I/II clinical trials should assess the safety, tolerability and preliminary efficacy of PRP-LWP formulations in patients with early-to-moderate knee OA. Study designs should include appropriate controls (PRP alone, LWPs alone, placebo) and standardized outcome measures (WOMAC, KOOS, VAS, MRI-based cartilage assessment). Pharmacokinetic studies should characterize intra-articular growth factor concentrations over time. Long-term follow-up (24-36 months) should assess durability of benefit and effects on disease progression.

Optimization and standardization of formulations. Systematic investigation of formulation parameters-including LWP molecular weight, concentration, source (marine, bovine, porcine), PRP preparation method, activation protocol and delivery vehicle should be conducted to identify optimal combinations. Regulatory considerations for combination products should be addressed early in the development process.

Conclusion

This systematic review synthesizes current evidence on the biochemical mechanisms underlying potential interactions between low-molecular-weight collagen peptides and platelet-rich plasma in joint therapy. The key findings and implications are summarized as follows:

- The canonical GPVI signaling pathway involving Syk, PLCγ2 and Ca^{2+} mobilization represents a well-characterized target for pharmacological modulation with established precedent for peptide-based inhibition
- PRP demonstrates time-dependent growth factor release profiles that can be extended through fibrin-based delivery systems, while LWPs exhibit chondroprotective and anti-inflammatory effects in preclinical models
- Clinical studies confirm symptomatic improvement with PRP in early-to-moderate knee osteoarthritis, though effect durability remains limited without repeat injection or enhanced delivery strategies
- The theoretical framework for LWP-PRP synergy is mechanistically plausible and supported by indirect evidence; however, direct experimental evidence for LWP modulation of GPVI signaling, effects on PRP release kinetics and synergistic therapeutic outcomes is currently absent
- Addressing this knowledge gap requires systematic investigation encompassing biochemical characterization of LWP-GPVI interactions, functional studies of platelet activation and growth factor release, preclinical efficacy studies in relevant animal models and ultimately well-designed clinical trials

The potential clinical benefits of optimized PRP-LWP formulations including prolonged growth factor bioavailability, enhanced chondrogenic activity and improved anti-inflammatory effects justify investment in this research program. Success in this endeavor could yield a next-generation biological therapy for osteoarthritis and other degenerative joint disorders, addressing the current limitations of conventional PRP while leveraging the complementary biological activities of collagen peptides.

Conflict of Interest

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Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Not applicable.

Authors' Contributions

All authors contributed equally to this paper.

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