

Recent Advancements in Platelet-Rich Concentrates

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Abstract

Platelet-rich concentrates (PRCs) have revolutionized the field of regenerative medicine by harnessing the body's intrinsic healing cascades. Derived from autologous blood, these biologic scaffolds deliver supraphysiologic doses of growth factors, cytokines, and leukocytes directly to sites of tissue injury. This narrative review explores the biological rationale underpinning PRCs, tracing their evolution from first-generation platelet-rich plasma (PRP) to second-generation platelet-rich fibrin (PRF) and beyond. Recent advancements have been systematically explored, encompassing low-speed centrifugation protocols such as Advanced Platelet-Rich Fibrin (A-PRF), injectable variants like Injectable Platelet-Rich Fibrin (i-PRF), and emerging third-generation platelet concentrates, including platelet-derived extracellular vesicles and exosomes. Furthermore, clinical applications across dentistry, periodontics, implantology, regenerative endodontics, orthopedics, and aesthetic medicine are discussed in detail. While contemporary PRCs offer significant advantages—including cost-effectiveness, immune compatibility, and robust tissue regeneration—challenges remain regarding protocol standardization, evidence heterogeneity, and variable clinical outcomes. By providing a comprehensive synthesis of current literature, this review aims to guide clinical decision-making and highlight critical avenues for future research in the pursuit of optimized, patient-specific regenerative therapies.

Keywords: platelet-rich plasma, platelet-rich fibrin, regenerative dentistry, wound healing, tissue engineering, exosomes, growth factors.

1. Introduction

Regenerative medicine has undergone a paradigm shift over the past two decades, transitioning from traditional grafting and synthetic biomaterials toward harnessing the patient's own biological healing mechanisms. Central to this evolution is the utilization of autologous platelet-rich concentrates (PRCs). Initially introduced in the 1990s as an adjunct to enhance bone grafts in maxillofacial surgery [1], PRCs represent a concentrated suspension of platelets, growth factors, and leukocytes suspended in a plasma or fibrin matrix. The fundamental rationale for their use lies in the natural role of platelets in hemostasis and wound healing; upon activation at an injury site, platelets degranulate and release a potent cocktail

of bioactive molecules that mediate tissue repair, angiogenesis, and stem cell recruitment.

This article serves as a narrative review aimed at synthesizing the expansive and rapidly evolving literature surrounding PRCs. As research has progressed, the processing of autologous blood has been refined to eliminate the need for biochemical additives, leading to the development of second-generation concentrates like Platelet-Rich Fibrin (PRF) [2]. More recently, alterations in centrifugation forces and hardware have birthed a multitude of novel derivatives tailored for specific clinical needs, ranging from solid matrices for bone grafting to injectable liquid formulations for deep tissue delivery. Despite their widespread adoption across diverse medical and dental disciplines, the field is often clouded by inconsistent terminology, variable preparation protocols, and conflicting clinical outcomes. This review comprehensively maps the biological basis, historical classification, recent technological advancements, clinical applications, and current limitations of PRCs, ultimately looking toward the horizon of next-generation regenerative therapies.

2. Biological Basis of Platelet-Rich Concentrates

The therapeutic efficacy of PRCs is inextricably linked to the physiological function of platelets and the intricate cascade of wound healing. Platelets are anucleate cellular fragments derived from megakaryocytes in the bone marrow. While traditionally recognized exclusively for their role in primary hemostasis, it is now well established that they are critical orchestrators of the inflammatory and proliferative phases of tissue regeneration.

Within their cytoplasm, platelets house three distinct types of secretory granules: alpha (α) granules, dense (δ) granules, and lysosomes. The α -granules are the most abundant and are the primary reservoir of bioactive proteins [5]. Upon tissue injury and subsequent platelet activation, these granules undergo exocytosis, releasing a supraphysiologic concentration of growth factors. Key molecules include Platelet-Derived Growth Factor (PDGF), which stimulates the mitogenesis and chemotaxis of mesenchymal stem cells and osteoblasts; Transforming Growth Factor-beta (TGF- β), a powerful regulator of extracellular matrix synthesis and immune response; Vascular Endothelial Growth Factor (VEGF), the primary driver of angiogenesis; and Epidermal Growth Factor (EGF), which promotes epithelialization [17].

Beyond growth factors, the biological architecture of the concentrate itself plays a pivotal role. First-generation PRCs relied on artificial activation (e.g., bovine thrombin and calcium chloride), resulting in a sudden burst release of growth factors that often did not align with the prolonged timeline of tissue remodeling. Conversely, the fibrin matrix formed in second-generation PRCs acts as a natural, three-dimensional biologic scaffold. This fibrin network traps platelets and leukocytes, protecting growth factors from rapid proteolytic degradation and allowing for their sustained release over a period of 7 to 14 days, which closely mimics the natural physiological healing process [8]. Additionally, the inclusion of leukocytes—particularly neutrophils and macrophages—confers antimicrobial properties and aids in the transition from the inflammatory to the reparative phase of healing through the secretion of pro- and anti-inflammatory cytokines.

3. Classification and Evolution of Platelet-Rich Concentrates

The rapid proliferation of platelet-derived products has led to a confusing nomenclature. To bring order to the field, several classification systems have been proposed. Dohan Ehrenfest et al. [3] established a widely accepted framework based on two key parameters: the presence or absence of a cellular

leukocyte population, and the fibrin architecture (low density vs. high density). This resulted in four main categories: Pure Platelet-Rich Plasma (P-PRP), Leukocyte- and Platelet-Rich Plasma (L-PRP), Pure Platelet-Rich Fibrin (P-PRF), and Leukocyte- and Platelet-Rich Fibrin (L-PRF). Another notable system is the PAW classification proposed by DeLong et al. [4], which categorizes PRP based on Platelet concentration, Activation method, and White blood cell content.

Historically, the evolution of PRCs is categorized into distinct generations. First-generation products, encompassing PRP and Plasma Rich in Growth Factors (PRGF), require the use of anticoagulants during blood collection to prevent premature clotting [1]. The plasma is separated via centrifugation and subsequently activated using exogenous agents. While effective at delivering growth factors, the lack of a robust fibrin scaffold and the use of chemical additives present notable drawbacks. To overcome these limitations, Choukroun et al. [2] developed the second-generation platelet concentrate, PRF. By omitting anticoagulants and utilizing a single-step centrifugation process, the natural coagulation cascade is allowed to proceed. This results in a dense, resilient fibrin clot that integrates platelets and leukocytes, eliminating the risks associated with bovine thrombin and enhancing the sustained release of regenerative cytokines.

4. Recent Advancements in Platelet-Rich Concentrates

In recent years, an enhanced understanding of centrifugation dynamics has catalyzed a renaissance in PRC formulations. Researchers discovered that standard high-speed centrifugation forces heavily push heavier cells (like leukocytes) to the bottom of the tube, limiting their incorporation into the therapeutic upper layers. By manipulating relative centrifugal force (RCF), time, and tube materials, new derivatives have been optimized for distinct biological functions [8].

4.1 Advanced PRF and Low-Speed Centrifugation Concepts

Advanced Platelet-Rich Fibrin (A-PRF) represents a significant protocol modification based on the “Low-Speed Centrifugation Concept” (LSCC). By reducing the centrifugation speed (e.g., 1500 rpm for 14 minutes or 1300 rpm for 8 minutes in A-PRF+), the physical stress on cells is minimized. This reduction in G-force prevents the heavier leukocytes and platelets from being driven deep into the red blood cell layer [14]. Consequently, A-PRF exhibits a more porous fibrin network and a significantly higher concentration of evenly distributed neutrophils and macrophages. In vitro studies confirm that A-PRF releases a higher total quantity of growth factors (such as TGF- β 1, VEGF, and PDGF) over a longer duration compared to traditional L-PRF, enhancing its regenerative and antimicrobial potential [8, 14].

4.2 Injectable PRF (i-PRF)

While solid PRF matrices are excellent for grafting and socket preservation, their dense nature prevents injection into deep tissues, joints, or aesthetic facial planes. To address this, Injectable PRF (i-PRF) was developed. i-PRF is produced by utilizing even lower centrifugation speeds (e.g., 700 rpm for 3 minutes) in plastic tubes devoid of clot-activating silica or glass components [10]. This precise parameter delays fibrin polymerization, maintaining the concentrate in a liquid state for approximately 15 to 20 minutes. i-PRF is rich in platelets, leukocytes, and circulating mesenchymal stem cells. Once injected, it undergoes spontaneous coagulation within the tissue, forming a dynamic fibrin scaffold in situ. Over the past decade, i-PRF has shown remarkable efficacy as a standalone injectable for soft tissue rejuvenation, joint therapy, and as an autologous binder for particulate bone grafts [11].

4.3 Concentrated Growth Factor, Titanium-PRF, Horizontal PRF, and Related Derivatives

Further iterations of the PRF protocol have introduced deliberate variations in centrifugation programmes, tube materials, and collection geometry in an attempt to improve cell capture, fibrin organisation, and clinical handling. Each derivative represents a distinct philosophy: some target a denser, longer-lasting scaffold; others prioritise maximum cellular yield; still others exploit tube-surface chemistry or rotor mechanics. The principal techniques are described individually below.

4.3.1 Concentrated Growth Factor (CGF)

Concentrated Growth Factor (CGF) was introduced by Sacco (2006) as a modification of PRF using a programmable centrifuge that alternates between two speeds (2,400 rpm and 2,700 rpm) during the processing cycle. This variable acceleration–deceleration protocol subjects blood cells to differential centrifugal forces, producing a distinctly dense fibrin block characterised by a thick, elastic consistency and a markedly high content of platelets, leukocytes, and – in several investigations – a relatively enriched population of CD34+ circulating progenitor cells compared with conventional fixed-speed PRF [17, 18]. The structural density of CGF arises from the more compact and cross-linked fibrin network formed during variable-speed centrifugation, which entraps cellular elements more firmly and may prolong the controlled release of growth factors such as transforming growth factor-beta 1 (TGF- β 1), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF-1) compared with standard-speed products [17, 19].

Clinically, CGF has been extensively investigated in maxillofacial and implant surgery. Its high mechanical resistance makes it suitable for space-maintaining applications such as lateral window sinus augmentation, where it can be positioned as a membrane substitute or mixed with bone substitutes to reduce the need for exogenous membranes [17]. In extraction socket management and alveolar ridge preservation, CGF has demonstrated accelerated socket fill and improved keratinised tissue maturation. Studies in periodontal intrabony and furcation defects have reported greater radiographic bone gain when CGF was combined with open-flap debridement or grafting versus grafting alone [18]. In implantology, CGF placed around implant fixtures has been associated with reduced marginal bone loss and improved peri-implant soft tissue contours at short-term follow-up [19]. Despite this encouraging body of evidence, most studies remain single-centre, small in scale, and heterogeneous in outcome measurement, limiting level-of-evidence conclusions. Standardised protocols for CGF preparation using validated centrifuge programmes are still lacking, which complicates cross-study comparisons [17, 18].

4.3.2 Titanium-Platelet-Rich Fibrin (T-PRF)

Titanium-Platelet-Rich Fibrin (T-PRF) was developed by Tunali et al. (2014) as a response to theoretical concerns regarding the safety profile of silica-coated glass Vacutainer tubes used in conventional PRF production. The central observation was that silica particles released from tube walls during centrifugation might theoretically be incorporated into the fibrin clot, raising biocompatibility questions in certain regenerative applications [20]. T-PRF substitutes the conventional borosilicate glass tube with a titanium metal tube whose inner surface triggers natural platelet activation and fibrin polymerisation exclusively through contact with titanium, a material universally acknowledged for its outstanding osseointegration properties and non-immunogenic profile.

Macroscopically, T-PRF clots tend to be substantially thicker and more robust than L-PRF membranes prepared under equivalent centrifugation conditions, a feature attributed to the titanium surface chemistry promoting a more organised fibrin polymerisation cascade. Scanning electron microscopy studies have demonstrated that the fibrin fibres in T-PRF are thicker and more densely interwoven than

in glass-tube PRF, producing a matrix that may be more resistant to enzymatic degradation and therefore persist longer in the regenerative site [20]. This prolonged scaffold lifespan is potentially advantageous in guided bone regeneration (GBR), where membrane integrity must be maintained throughout the early phase of osteogenesis. In vitro studies comparing growth factor release kinetics have suggested that T-PRF releases PDGF-AB, TGF- β 1, and VEGF over an extended time course compared with standard L-PRF, consistent with its denser fibrin architecture [20]. Clinical investigations have evaluated T-PRF in extraction socket healing and soft tissue management, with histological observations suggesting favourable angiogenesis and connective tissue maturation. However, the evidence base for T-PRF remains limited in volume; the majority of publications are from a small number of research groups, and large-scale randomised controlled trials comparing T-PRF with established PRF protocols are still awaited [20].

4.3.3 Horizontal PRF (H-PRF)

Horizontal PRF (H-PRF) was described by Miron et al. (2019) as a protocol modification based on centrifuge rotor mechanics rather than a change in blood processing chemistry. Conventional PRF is prepared in fixed-angle centrifuges, where tubes are held at a constant inclined angle relative to the rotor axis. During centrifugation, the angled orientation causes sedimenting cells to strike the lower tube wall, which may cause mechanical shearing and result in sub-optimal recovery of the platelet and leukocyte layer. In a horizontal (swing-out) rotor, the tubes swing to a position perpendicular to the rotor axis once rotation commences, so cells sediment along the true longitudinal axis of the tube in alignment with the applied centrifugal force. This geometry more closely replicates an idealised density-gradient separation, reducing wall-impact cell loss and theoretically delivering a higher and more homogeneous yield of the buffy-coat fraction [21].

Comparative studies examining platelet count, leukocyte count, and fibrin architecture in H-PRF versus fixed-angle PRF under matched centrifugation parameters have reported that H-PRF membranes contain a significantly greater total number of platelets and CD68⁺ macrophage precursors, and that the fibrin network is more uniformly porous, which may benefit cell infiltration and revascularisation of the clot in vivo [21]. Growth factor quantification studies have reported higher concentrations of VEGF, TGF- β 1, EGF, and PDGF in H-PRF exudate compared with fixed-angle L-PRF controls prepared simultaneously from the same blood draw [21]. Clinically, H-PRF membranes have been explored in extraction socket preservation, gingival recession coverage, and sinus augmentation with preliminary outcomes suggesting non-inferiority or superiority to standard PRF. However, the evidence remains early-phase, and the lack of commercially standardised horizontal centrifuges calibrated for PRF preparation constitutes a current translational barrier [21].

4.3.4 Advanced PRF Plus (A-PRF+)

A-PRF+ is a refinement of the original A-PRF concept incorporating an even lower centrifugation speed (1,300 rpm / approximately 200 x g) with a shortened spin time (8 minutes). The rationale is to maximise the retention of monocytes, macrophages, and neutrophils within the fibrin scaffold while simultaneously preserving platelet morphology by minimising shear stress [22]. In vitro analyses have demonstrated that A-PRF+ releases significantly higher cumulative levels of growth factors at 8 days compared with both A-PRF and conventional L-PRF, attributed to the higher leukocyte content continuously secreting cytokines as the clot is remodelled [22]. Macrophages within the A-PRF+ matrix are thought to polarise toward an M2 phenotype over time, shifting the regenerative microenvironment toward anti-inflammatory and pro-angiogenic signalling. A-PRF+ is particularly investigated for soft

tissue applications including gingival recession coverage and wound healing in medically compromised patients where prolonged growth factor availability is clinically important [22].

4.3.5 Concentrated PRF (C-PRF)

Concentrated PRF (C-PRF), also referred to as high-density PRF in some literature, is prepared using additional centrifugation steps or modified tube geometries designed to compress the final fibrin clot and increase the volumetric density of platelets and growth factors per unit area of membrane. The objective is to deliver a more potent biologic payload than standard-density PRF membranes without altering the fundamental absence of anticoagulants [23]. Experimental data suggest that C-PRF exhibits measurably higher concentrations of PDGF, TGF- β 1, and BMP-2 in release assays, making it of potential interest for osseous regeneration where high local growth factor concentrations are desirable. Standardised preparation protocols and prospective clinical data are currently limited.

4.3.6 Albumin-PRF

Albumin-PRF represents an experimental hybrid formulation in which platelet-rich fibrin is combined or co-processed with albumin solutions. The theoretical basis is that albumin, as the most abundant plasma protein, can modulate fibrin polymerisation kinetics, improve fibrin fibre diameter, and serve as an additional carrier matrix for growth factors [23]. The albumin fraction may also enhance the viscoelastic properties of the final scaffold, making it easier to handle surgically and potentially improving its durability at defect sites. Most published data on albumin-PRF are from laboratory characterisation studies; in vivo and clinical evidence is nascent, and this formulation should currently be regarded as an investigational derivative requiring further validation.

4.3.7 Summary and Comparative Perspective

Table 1: Comparative Overview of Advanced Platelet-Rich Concentrate Derivatives

Derivative	Centrifugation Protocol	Tube / Rotor	Key Structural Features	Growth Factor Profile	Primary Clinical Uses	Level of Evidence
CGF (Concentrated Growth Factor)	Variable speed 2,400 rpm $\rightarrow$ 2,700 rpm alternating cycles	Glass/silica tube; Fixed-angle rotor	Dense elastic fibrin; CD34+ progenitor cells enriched; thick fibrin fibres	Prolonged TGF- β 1, PDGF, VEGF, IGF-1 release; higher entrapment than L-PRF	Sinus augmentation; socket preservation; periodontal defects; peri-implant regeneration	Moderate (controlled studies and RCTs; heterogeneous)
T-PRF (Titanium-PRF)	Single-step ~2,700 rpm / 12 min (standard L-PRF protocol)	Titanium metal tube; Fixed-angle rotor	Thicker, denser fibrin fibres on SEM; no silica contact; longer scaffold persistence	Extended PDGF-AB, TGF- β 1, VEGF release vs. L-PRF	GBR (membrane substitute); extraction socket; implant site development	Limited (mainly in vitro + small single-centre clinical studies)
H-PRF (Horizontal)	Low-speed ~1,500 rpm	Plastic tube;	Homogeneous fibrin architecture; higher	Higher VEGF, TGF-	Extraction socket;	Emerging (pilot RCTs;

PRF)	12 min	Swing-out (horizontal) rotor	platelet and leukocyte yield per unit volume	β 1, EGF, PDGF vs. fixed-angle PRF from same blood draw	gingival recession coverage; sinus augmentation	standardised centrifuge availability (limited)
A-PRF+ (Advanced PRF Plus)	Ultra-low speed ~1,300 rpm (approx. 200 x g) / 8 min	Glass or plastic tube; Fixed-angle rotor	Highly porous fibrin; maximum monocyte/macrophage retention; M2-polarisation microenvironment	Highest cumulative GF release at 8 days vs. A-PRF and L-PRF; strong anti-inflammatory cytokine profile	Soft tissue regeneration; gingival recession; wound healing in compromised hosts	Moderate (in vitro and small clinical trials)
C-PRF (Concentrated PRF)	Additional compression step or modified tube geometry post-centrifugation	Specialised compression device; Fixed-angle rotor	High-density fibrin; increased volumetric platelet/GF concentration per membrane area	Higher PDGF, TGF- β 1, BMP-2 concentration vs. standard-density PRF	Osseous regeneration; hard tissue defects requiring high local GF dose	Limited (mostly in vitro characterisation)
Albumin-PRF	Co-processing with albumin solution during or after centrifugation	Standard tube + albumin supplement; Fixed-angle rotor	Modified fibrin fibre diameter; enhanced viscoelasticity; albumin additional carrier	Modulated fibrin polymerisation; potentially improved GF retention and scaffold durability	Investigational; early-phase laboratory and animal studies	Very limited (preclinical / laboratory only)

Collectively, the CGF, T-PRF, H-PRF, A-PRF+, C-PRF, and albumin-PRF derivatives illustrate that the evolution of platelet-rich concentrates is no longer driven solely by platelet enrichment ratios but by the deliberate engineering of fibrin architecture, cellular composition, and growth factor release kinetics for defined clinical contexts. The selection of a specific derivative should ideally be guided by the biological requirements of the target tissue, the available centrifuge equipment, and, increasingly, by evidence from well-designed randomised controlled trials rather than in vitro data alone [17, 18, 20, 21, 22, 23]. Table 1 provides a comparative summary of these advanced derivatives.

4.4 Platelet Lysate, Lyophilized Products, and Biomaterial Combinations such as Sticky Bone

Efforts to increase storage stability and broaden practical use have led to the development of platelet lysate (PL) and lyophilized platelet-rich products. Platelet lysate is typically produced through freeze-

thaw cycles, thermal disruption, or sonication, which rupture platelet membranes and release soluble growth factors, cytokines, and other bioactive contents into a cell-free preparation. This approach is attractive because it reduces dependence on intact platelet viability at the time of use and may provide a more standardized soluble biologic fraction for research, cell culture, and selected regenerative applications [12, 13]. Lyophilized PRF and related freeze-dried products are intended to improve transport and shelf life while preserving at least part of the scaffold and signaling activity, although the extent to which drying and reconstitution alter clot architecture and biologic potency still requires careful evaluation.

Another clinically important advancement is the integration of PRCs with grafting biomaterials. The best-known example is sticky bone, in which i-PRF or another liquid fibrin-rich fraction is combined with particulate grafts so that fibrin polymerization binds the particles into a cohesive mass. This improves handling, reduces particle migration, and provides a biologically active matrix that can be adapted to extraction sockets, ridge defects, and sinus augmentation sites [10, 11]. Similar combination strategies now include PRF membranes layered over grafts, PRF exudate used to hydrate biomaterials, and hybrid constructs incorporating collagen, xenografts, or alloplasts. These approaches are particularly relevant because many modern clinical protocols do not use PRCs as standalone products; instead, they use them as bioactive adjuncts that improve the handling and healing profile of conventional regenerative materials [6, 10, 15].

4.5 Platelet-Derived Extracellular Vesicles and Exosomes as Emerging Third-Generation Concepts

The frontier of platelet concentrate research is currently shifting from cellular therapies to cell-free, nanoscale interventions, heralding what some authors described as a third generation of platelet-derived products [16]. Platelet-derived extracellular vesicles (p-EVs), including exosomes and microparticle-like fractions, are membrane-bound nanoparticles released during platelet activation. Rather than acting as simple debris, these vesicles function as biologic messengers that transport proteins, lipids, messenger RNA, and microRNA to recipient cells, thereby influencing angiogenesis, inflammation, matrix remodeling, and stem-cell behavior. Their appeal lies in the possibility of reproducing key regenerative signaling pathways without depending on whole-cell preparations or bulky fibrin clots.

From a translational standpoint, exosome-oriented products may offer advantages in dose standardization, storage, and targeted delivery, and they may eventually be incorporated into coatings, hydrogels, or injectable regenerative formulations. However, this field remains early in development. Important unresolved issues include isolation methods, purity thresholds, dosing strategies, regulatory classification, and the need to confirm long-term safety and efficacy in robust clinical trials. Therefore, although platelet-derived extracellular vesicles are among the most exciting recent advancements in the field, they should currently be interpreted as promising investigational platforms rather than routine clinical substitutes for established PRP or PRF protocols [12, 16].

5. Current and Expanding Clinical Applications

The versatile biological properties of PRCs have facilitated their widespread integration into numerous medical and surgical disciplines.

Dentistry, Oral Surgery, and Implantology: PRCs are extensively utilized to accelerate soft tissue closure and enhance bone maturation following tooth extractions, preventing alveolar osteitis (dry socket). In implantology, PRF membranes are employed in sinus lift procedures, guided bone

regeneration (GBR), and peri-implant defect repair. The combination of PRF with bone substitutes (Sticky Bone) accelerates osseointegration and improves graft stability [6, 7, 13, 15].

Periodontics: In the management of periodontal disease, PRF is used as an adjunct to open flap debridement and in the treatment of intrabony defects. Furthermore, PRF membranes serve as a viable alternative to connective tissue grafts for the coverage of localized gingival recessions, significantly reducing donor-site morbidity [7].

Regenerative Endodontics: A pivotal advancement in endodontics is the use of PRPs and PRFs as biologic scaffolds for the revitalization of immature permanent teeth with necrotic pulps. PRF provides an ideal matrix that supports the migration and proliferation of apical papilla stem cells, promoting continued root development and dentinogenesis [9].

Wound Healing: In chronic and refractory wounds, such as diabetic foot ulcers and venous leg ulcers, topically applied PRF acts as a protective biologic dressing that continuously bathes the wound bed in angiogenic factors, rapidly inducing granulation tissue formation and epithelialization [10, 11].

Orthopedics and Sports Medicine: Intra-articular injections of liquid PRPs and i-PRF are widely adopted for the conservative management of osteoarthritis, tendinopathies, and ligamentous injuries. The anti-inflammatory cytokines within the concentrates modulate the joint microenvironment, reducing pain and stimulating chondrocyte proliferation.

Dermatology and Aesthetic Medicine: The regenerative capacity of i-PRF is increasingly utilized in facial aesthetics for the treatment of rhytids, photoaging, and acne scarring. Furthermore, microinjections of i-PRF into the scalp have demonstrated promising results in the stimulation of hair follicles for the treatment of androgenetic alopecia [11].

Table 2: Comparative Overview of Major Platelet-Rich Concentrate Systems

Concentrate Generation/Type	Preparation Concept	Main Characteristics	Release Profile	Typical Clinical Uses
First Gen: PRP / PRGF	Anticoagulants used; multiple spins; exogenous activation (thrombin/calcium).	Liquid suspension; variable leukocyte count; no natural fibrin scaffold.	Rapid burst release of growth factors (hours to days).	Joint injections, sports injuries, early bone graft mixing.
Second Gen: L-PRF	No anticoagulants; single high-speed spin (~3000 rpm); natural coagulation.	Solid, dense fibrin matrix; rich in platelets and leukocytes.	Slow, sustained release (7 to 14+ days).	Extraction socket preservation, sinus lifts, periodontal defects.
Modified Second Gen: A-PRF / A-PRF+	Low-speed centrifugation concept (LSCC); lower RCF.	Highly porous fibrin; enhanced leukocyte retention and uniform distribution.	Prolonged, elevated release of growth factors vs. traditional L-PRF.	Gingival recession coverage, soft tissue regeneration, wound care.
Liquid/Injectable: i-PRF	Low speed (~700 rpm); short duration; no glass/silica to delay clotting.	Liquid state (15–20 mins) before forming a clot in situ; high stem cell content.	Sustained in vivo release once polymerized.	Facial aesthetics, alopecia, osteoarthritis, “Sticky Bone” preparation.
Third Gen: Platelet	Cell rupture (freeze-	Cell-free;	Immediate	Pre-clinical

Exosomes Lysates	(thaw) or exosome isolation via ultracentrifugation.	concentrated bioactive lipids, miRNAs, and proteins.	availability of signaling molecules; highly targetable.	regenerative medicine, standardized off-the- shelf therapies.
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6. Advantages of Contemporary Platelet-Rich Concentrates

The contemporary iterations of PRCs, particularly the anticoagulant-free second-generation formulations, offer profound advantages. Primarily, their autologous nature eliminates the risk of cross-infection, immunogenic rejection, and foreign body reactions [13]. From a practical standpoint, the preparation of PRF and its derivatives is simple, rapid, and highly cost-effective, requiring only basic venipuncture equipment and a desktop centrifuge, making it accessible for routine clinical practice. Biologically, the natural fibrin architecture of PRF acts as an optimal biomimetic scaffold. It not only protects growth factors from rapid enzymatic degradation but also facilitates cell homing, acting as a provisional extracellular matrix that guides migrating fibroblasts and endothelial cells. The inherent presence of leukocytes provides an autologous immune defense mechanism, mitigating postoperative infection risks and orchestrating the complex inflammatory signaling required for true tissue regeneration.

Table 3: Summary of Recent Technical Advancements in Platelet-Rich Concentrate Preparation and Their Clinical Implications

Advancement	Technical Modification	Practical Clinical Implication
Low-Speed Centrifugation (A-PRF)	Reduced G-force preserves heavier cell populations.	Yields a more cellular scaffold with enhanced antimicrobial and healing properties, ideal for infected or compromised wound beds.
Liquid PRF (i-PRF)	Delaying the coagulation cascade using specific plastic tubes.	Allows minimally invasive injection into joints, dermis, and root canals, and enables the creation of moldable “Sticky Bone” grafts.
Horizontal Centrifugation	Swing-out rotors prevent cells from accumulating on tube walls.	Produces a larger, more homogeneous fibrin clot with a higher total yield of usable biological material.
Platelet Lysates & Lyophilization	Physical cell lysis and freeze-drying of the plasma product.	Resolves shelf-life limitations, allowing clinicians to prepare and store standardized doses of growth factors for sequential treatments.

7. Limitations, Controversies, and Standardization Challenges

Despite their immense promise, the translation of PRCs into universally accepted gold-standard therapies is hindered by several limitations. The foremost challenge is the sheer heterogeneity of the evidence base [12, 15]. The biological quality of PRCs is highly dependent on patient-specific variables,

including age, systemic health, nutrition, and hematologic profile. Consequently, the concentration of growth factors can vary wildly from patient to patient, leading to inconsistent clinical outcomes. Furthermore, a lack of standardization in preparation protocols plagues the literature. Variations in centrifuge rotor angulation, tube size, tube material (glass vs. plastic vs. silica-coated), RCF, and processing time drastically alter the physical and biological characteristics of the final product [8, 12]. This methodological inconsistency makes it exceedingly difficult to conduct high-quality meta-analyses or establish definitive clinical guidelines. Additionally, while the retention of leukocytes in PRF is generally considered beneficial for antimicrobial defense, some researchers argue that an excess of neutrophils may exacerbate tissue destruction through the release of reactive oxygen species and matrix metalloproteinases in certain inflammatory conditions [12]. Finally, outcome reporting in clinical trials is often short-term and relies on surrogate radiographic or clinical markers rather than true histologic evidence of regeneration.

8. Future Perspectives

The future of platelet-rich concentrates lies in the dual pursuit of standardization and advanced bioengineering. To mitigate variability, the development of closed, automated processing systems equipped with optical sensors could allow for the precise, reproducible isolation of specific cellular fractions regardless of patient baseline hematology. There is also a critical need for large-scale, multicenter randomized controlled trials utilizing unified nomenclature (such as the Ehrenfest or PAW classifications) to clearly define which specific PRC formulation is optimal for distinct clinical indications.

On the molecular frontier, the integration of PRCs with advanced biomaterials—such as 3D-printed hydrogels, electrospun nanofibers, and functionalized nanoparticles—will likely yield hybrid smart scaffolds capable of spatiotemporally controlled growth factor release. Moreover, the transition toward third-generation cell-free therapies, specifically platelet-derived exosomes, holds transformative potential [16]. By isolating and concentrating the precise molecular cargo responsible for regeneration, researchers aim to develop potent, standardized, and shelf-stable biologics that circumvent the unpredictability inherent in whole-cell autologous concentrates.

9. Conclusion

Platelet-rich concentrates have established themselves as an indispensable tool in the armamentarium of modern regenerative medicine. The evolution from first-generation PRP to the robust, naturally coagulating scaffolds of PRF, and further to highly specialized liquid and low-speed formulations, underscores a continuous refinement in harnessing autologous healing biology. As evidenced by their successful integration into dentistry, periodontics, endodontics, and orthopedics, PRCs offer a safe, autologous, and cost-effective means of accelerating tissue repair and bone regeneration. Nevertheless, to fully unlock their clinical potential, the scientific community must address the ongoing challenges of protocol standardization and biologic variability. By advancing toward precision processing and exploring emerging exosome-based technologies, the next generation of platelet-derived therapies promises to deliver increasingly predictable, targeted, and powerful regenerative outcomes.

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