Received: 10 November 2023 | Revised: 6 February 2024 | Accepted: 4 March 2024

DOI: 10.1111/prd.12563

Periodontology 2000 WILEY

REVIEW ARTICLE

Impact of autologous platelet concentrates on the osseointegration of dental implants

Sašo Ivanovski[1] | Ryan S. B. Lee[1] | Tulio Fernandez-Medina[1,2] | Nelson Pinto[3] | Catherine Andrade[3] | Marc Quirynen[4]

[1]School of Dentistry, Centre for Orofacial Regeneration, Reconstruction and Rehabilitation (COR3), The University of Queensland, Brisbane, Australia

[2]College of Medicine and Dentistry, James Cook University, Cairns, Australia

[3]Department of Periodontology and Implantology, Faculty of Dentistry, Universidad de Los Andes, Santiago, Chile

[4]Department of Oral Health Sciences, Katholieke Universiteit Leuven (Periodontology), University Hospitals Leuven, Leuven, Belgium

Correspondence
Sašo Ivanovski, School of Dentistry, The University of Queensland, Brisbane, Australia.
Email: s.ivanovski@uq.edu.au

Abstract

Osseointegration is defined as the direct deposition of bone onto biomaterial devices, most commonly composed from titanium, for the purpose of anchoring dental prostheses. The use of autologous platelet concentrates (APC) has the potential to enhance this process by modifying the interface between the host and the surface of the titanium implant. The rationale is to modify the implant surface and implant–bone interface via "biomimicry," a process whereby the deposition of the host's own proteins and extracellular matrix enhances the biocompatibility of the implant and hence accelerates the osteogenic healing process. This review of the available evidence reporting on the effect of APC on osseointegration explores in vitro laboratory studies of the interaction of APC with different implant surfaces, as well as the in vivo and clinical effects of APC on osseointegration in animal and human studies. The inherent variability associated with using autologous products, namely the unique composition of each individual's blood plasma, as well as the great variety in APC protocols, combination of biomaterials, and clinical/therapeutic application, makes it is difficult to make any firm conclusions about the in vivo and clinical effects of APC on osseointegration. The available evidence suggests that the clinical benefits of adding PRP and the liquid form of L-PRF (liquid fibrinogen) to any implant surface appear to be limited. The application of L-PRF membranes in the osteotomy site, however, may produce positive clinical effects at the early stage of healing (up to 6 weeks), by promoting early implant stability and reducing marginal bone loss, although no positive longer term effects were observed. Careful interpretation and cautious conclusions should be drawn from these findings as there were various limitations in methodology. Future studies should focus on better understanding of the influence of APCs on the biomaterial surface and designing controlled preclinical and clinical studies using standardized APC preparation and application protocols.

KEYWORDS
biomimicry, bone, L-PRF, PRP, titanium

1 | INTRODUCTION

Osseointegration is a complex process that involves a cascade of events occurring at the tissue–implant interface following the insertion of a biocompatible medical device, most commonly made of titanium, into the human body.[1] These events involve clot formation and the initial adsorption of serum components immediately following implant placement, an immune-inflammatory response to implant insertion, the migration and attachment of undifferentiated mesenchymal cells onto the implant surface, their proliferation and differentiation, the formation of extracellular matrix, and finally its mineralization and maturation.[1] These biological mechanisms have been described in various longitudinal studies in animals and humans, with a broad understanding that a rapid transition from an early inflammatory response to a reparative pro-osteogenic environment is essential for successful osseointegration.[2-4]

It is widely recognized that the characteristics of the implant surface are critical to the nature of the subsequent bone healing post-implantation. Surface topography in particular has been shown to be highly influential, with microrough surfaces being able to promote "contact" osteogenesis, whereby bone formation occurs directly on the implant surface, as distinct from "distance" osteogenesis that is associated with minimally rough (turned/machined) implant surfaces, whereby the bone formation occurs from the surface of the surgically created osteotomy bone margin toward the implant.[5] Contact osteogenesis is considered to be a desirable bone healing feature following implant insertion as the consequent early formation of direct bone–impact contact promotes the rapid establishment of "secondary" bone stability that is able to withstand functional forces, thus allowing for safe and predictable functional loading. Aside from surface topography, various other surface modifications, including chemical and biological approaches, have been utilized to enhance osseointegration.[6]

Irrespective of the nature of the implant surface, it is widely recognized that the initial interactions of blood proteins with the implant surface immediately following implantation are critically important in determining the subsequent wound healing biological events.[1] In this context, the use of platelet concentrates has the potential to modify the implant surfaces during the early stages of osseointegration and hence influence these downstream healing events.[7] It can be postulated that this surface modification utilizing autologous blood products, namely autologous platelet concentrates (APC), may act as a "biomimetic" coating on the biomaterial surface that enhances the biocompatibility of the dental implant (which is essentially a foreign body) by imparting extracellular matrix proteins and growth factors native to the recipient, thereby enhancing the rate and extent of bone formation during the osseointegration process.

The use of blood products in clinical practice for tissue healing improvement has been reported for more than six decades.[8] Different protocols use various blood plasma fractionation approaches through centrifugation to obtain three main components: plasma, buffy coat, and red blood cells.[9] The anabolic properties of hemoderivatives depend on the secretion of cytokines and chemokines from the platelet-α-granules and from the fibrin network interaction. Due to their autologous origins, hemoderivatives have generated considerable interest in both the clinical setting and more recently in osseointegration.[10] Furthermore, growth factors such as bone morphogenetic protein 2 (BMP-2), platelet-derived growth factor beta–beta (PDGF-BB), and vascular endothelial growth factor (VEGF), as well as fibrin matrix proteins are found in blood products at a superior dose to that of blood and are hypothesized to directly contribute to enhanced osteogenesis.[11]

The general content at the blood protein–biomaterial interface has been investigated and it is mainly composed of blood plasma proteins, such as albumin, coagulation factors, complement system, immunoglobulins, lipoproteins, other plasma components, and tissue leakage proteins.[12] The characteristics of the substrate, such as topography and surface energy, may directly influence the mechanism of protein adsorption, ranging from weak bonds (i.e., Van der Waals interactions) to stronger electrostatic interactions.[13] The inherent complexity in the biomaterial–protein interface makes it difficult to elucidate the precise interplay of protein adsorption and its subsequent effect on cells. Although controlling protein adsorption in vivo is difficult, a recent study has highlighted the importance of tailoring the protein adsorption on implantable devices.[14] By controlling the chemistry, morphology and topography of the biomaterial surface, a shift in the protein adsorption from opsonins (accelerate phagocytosis) to dysopsonins (retard phagocytosis) can be achieved which may result in the attenuation of the immune response at the biomaterial interface.[14] As blood rapidly encounters biomaterial devices, it is important to understand how blood proteins interact with biomaterial surfaces leading to superior osseointegration.

This review explores the nature of platelet concentrate–implant interaction and how the interaction between different implant surfaces and various platelet concentrate formulations can subsequently influence osseointegration. The available evidence for the influence of APC in osseointegration is outlined by reviewing in vitro, preclinical and clinical studies that investigate the effect of APC on osseointegration.

2 | LABORATORY TESTS ON BIOFUNCTIONALIZATION OF IMPLANT SURFACES WITH APCs

Several in vitro studies were identified which explored the interaction of APC with implant surfaces, utilizing a range of APC preparations and experimental assays (Table 1). Generally, it was demonstrated that APC are able to positively enhance the bioactivity of implant surfaces. Sanchez-Ilarduya et al.[15] investigated the kinetics of growth factor release at pure grade IV titanium discs functionalized with PRGF (nonactivated, activated with Ca, or with Ca/thrombin), and correlated the results with the morphology of the resulting interfaces. The main finding was that plasma rich in growth factors (PRGF) activation and clot formation favors longer retention times of the growth factors at the implant interfaces, likely due to their retention in the adsorbed fibrin matrix.

TABLE 1 Laboratory (in vitro) studies on the interaction of implant surfaces and APC.

Study	Surface	Follow up	APC protocol/cell supplement	Anticoagulant	Outcomes
Sanchez-Ilarduya et al.[15]	Rough cp Ti-IV	1, 48 h 4 and 9 days	Platelet rich in growth factors (PRGF): 580*g* for 8 min. Platelet-poor plasma (PpP): 4500*g* for 6 min at RT	3.8% (wt/vol) sodium citrate. Calcium activated (Ca), calcium/thrombin activated (CaT), and nonactivated (NA) groups	Thrombin activation does not affect growth factors retention but decrease their release. There were more platelets and thicker fibrils in PRGF group than PPP. PDGF, TGF-B1, and VEGF release were superior to those on PPP, but these differences were not statistically significant ($p > 0.05$)
Lee et al.[16]	Standard Ti6A14V rough, grit-blasted (TiGB)	80 min incubation 14 and 21 days on cell culture	150*g* for 10 min. Human osteoblasts seeding on surface	N/R	Fourfold capacity of platelet adhesion on TiGB surfaces versus tissue culture plates (control) and threefold capacity on Ti-surface when PRP was added. ALP (fourfold) and calcium content (threefold) were higher on PRP-supplemented surfaces ($p < 0.05$)
Lollobrigida et al.[17]	Rough and smooth cp Ti-IV	8 min	2700 rpm for 12 m (L-PRF), take the fibronectin and vitronectin exudate from clots. 2037 *g* for 9 m (PLyF-concentrate)	None (fresh blood)	Fibronectin and vitronecton exudate on rough Ti presented a thicker fibrin network. PLyF concentrate seems to produce a thinner and fragile fibrin mesh on Ti surfaces
Zhang et al.[18]	TNT coating annealed at 350°C, 450°C, and 550°C	30 and 60 min	210*g* for 10 min. Collect supernatant and re-spin another 210*g* for 10 min	3.2% (wt/vol) sodium citrate	Group annealed at 450°C (4719 ± 86) produced the highest release of PDGF (pg/mL) followed by 350°C (4488 ± 74), 550°C (4400 ± 82), and unannealed (4241 ± 74) ($p < 0.05$)
Irastorza et al.[19]	Standard Ti6A14V and biomimetic BAS™ (Avinent Implant System)	60 min incubation 14 days cell culture	Plasma rich in growth factors (PRGF): 580*g* for 8 min at RT. After activation 3000*g* for 15 min. Platelet rich fibrin (PRF): 580*g* for 8 min at RT. To supplement Human pulp stem cells (hDPSCs)	3.8% (wt/vol) sodium citrate. 10% calcium chloride activation	Osteogenic commitment of hDPSCs seeded on different surfaces when either PRGF or PRF were supplemented (gene expression of RUNX2, SPARC, OSTERIX/SP7, RUNX2, and SPARC; $^{*}p \leq 0.05$). Mature osteoblastic marker (OSTERIX) was only detected in the presence of PRF
Andrade et al.[20]	OsseoSpeed™ (Astra Tech); TiUnite™ (Nobel Biocare™); SLActive® (ITI Straumann); Ossean® (Intra-Lock®); Plenum®	60 min at RT	2700 rpm for 3 min (liquid fibrinogen)	None (fresh blood)	Fiber thickness and density fibrin mesh were clearly higher in Ossean® and Plenum® surfaces. Fibers on Osseospeed™, TiUnite™, and SLAc-active® were observed mostly parallel to the implant axis. Characteristics such as topography, wettability, and coatings influence the interaction between the implant surface and fibrin

Abbreviations: ALP, alkaline phosphatase; cp Ti-IV, commercially pure titanium IV; OSTERIX, transcription factor Sp7, also called osterix; PDGF, platelet-derived growth factor; PLyF, platelets, lymphocytes, and fibrinogen liquid concentrate; PpP, platelet-poor plasma; PRP, platelet-rich plasma; RT, room temperature; RUNX2, Runt-related transcription factor 2; SPARC, secreted protein acidic and rich in cysteine; TGF-B1, transforming growth factor beta-1; TNT, titanium nanotubes; VEGF, vascular endothelial growth factor.

It is evident that not all implant surfaces react in a similar fashion to the application of an APC. Lollobrigida et al.[17] coated six commercial pure titanium discs (three with a micro/nanorough Ossean® and three minimally rough surfaces) via three different protocols: (a) 10 min immersion in liquid fibrinogen, (b) 5 min immersion in L-PRF exudate, and (c) 2 min immersion in L-PRF exudate followed by 8 min in liquid fibrinogen. Scanning electron microscopy revealed that coating with liquid fibrinogen resulted in a dense fibrin network in direct contact with the implant surface trapping a number of WBC and some RBC (Figure 1). In contrast, coating with L-PRF exudate did not lead to a fibrin network, and only a small number of WBC and RBC adhered to the titanium surface, while coating with both L-PRF exudate and liquid fibrinogen resulted in an apparent increase in the thickness of the fibrin layer. The micro/nanorough surface showed an increased retention of fibrin, leading to a thicker coating compared to the minimally rough surface.

Andrade et al.[20] explored the first steps in the formation of a fibrin network on different commercial implants with typical surface characteristics (Astra Tech Osseospeed, Nobel Biocare TiUnite, Straumann SLActive, Intra-Lock Ossean, and Plenum 3-D printed surface). Each implant was soaked in liquid fibrinogen for 60 min, fixed in 2% glutaraldehyde, and prepared for scan electron microscopy (SEM) (Figure 2). SEM identified significant differences between the implant surfaces. The quality of the fibrin matrix was clearly implant surface dependent. While some implants (Osseospeed, TiUnite, and SLActive surface) were only partially covered with a fibrin layer, the Ossean and Plenum surfaces were fully packed in a dense fibrin network. The latter surfaces also showed a denser and more uniform layer of fibrin that under higher magnification seemed to follow the threats closely. Furthermore, the thickness of the fibrin fibers and density of the fibrin mesh also seemed higher on the Ossean and Plenum surfaces. The fibrin fibers on the Osseospeed, TiUnite, and SLActive surface were mostly running parallel to the implant surface, whereas for the Ossean and Plenum surface several fibrin fibers tended to run perpendicularly to the surface. In addition to this perpendicular attachment, the Plenum surface also showed a strong connection between fibrin fibers and the surface irregularities, something that was not seen on the other surfaces.

APC were also shown to have specific interactions with nanoscale surface modifications that could be sensitive to the surface

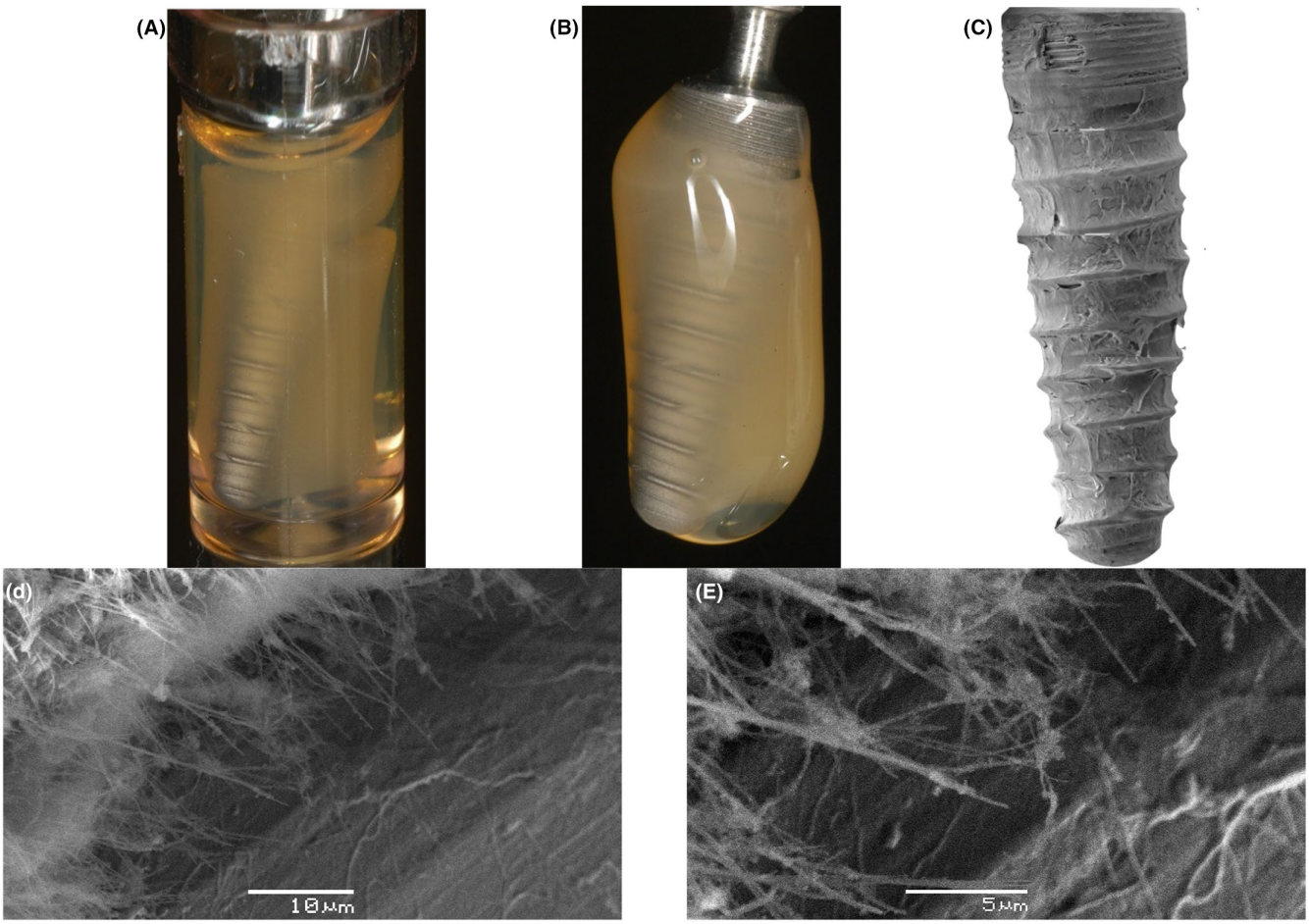

FIGURE 1 Protocol for the evaluation of fibrin network formation when dipping an implant in liquid fibrinogen. (A) Implant soaked in liquid fibrinogen for 60 min, (B) after careful removal of the implant, part of the liquid fibrinogen adhered to the implant, (C) SEM picture of the implant. Note the tight contact between the implant surface and the coating. (D, E) Under high magnification the fibrin matrix becomes more visible, with fibrin fibers running to/adhering to the implant surface.

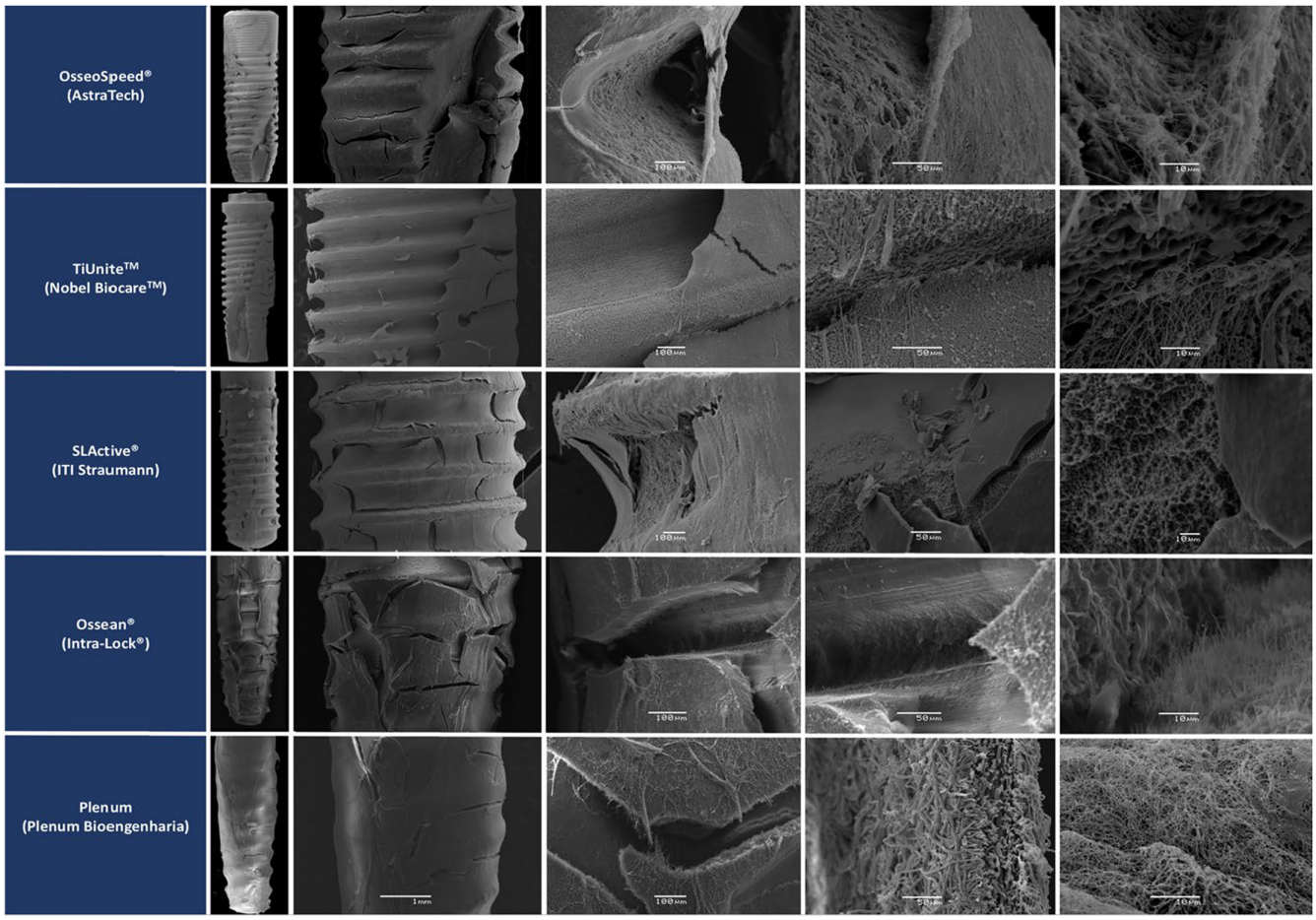

FIGURE 2 Fibrin matrix on different dental implants (identified in far left column), examined via SEM at increasing magnification from left to right (from Andrade et al.[20]).

preparation methods. The crystalline phases of titania (TiO_2) nanotube (TNT) coatings, achieved through anodization and subsequent annealing at 350°C, 450°C, and 550°C, were exposed to PRP with the aim of improving platelet adhesion and activation for enhanced osseointegration.[18] PRP was prepared by centrifugation of citrated human blood at 200*g* for 10 min. The top supernatant layer was retrieved and centrifugation was repeated using the same parameters, and subsequently incubated for 30 and 60 min to assess the number, viability, distribution, and morphology of the adhered platelets. Platelet P-selectin (CD62P) and PDGF expression were used to indicate platelet activation. The results revealed that the annealed group at 450°C (4719 ± 86) produced the highest release of PDGF (pg/mL) followed by 350°C (4488 ± 74), 550°C (4400 ± 82), and unannealed (4241 ± 74). Furthermore, the platelets on the 350°C and 450°C annealed TNT coating groups expressed the strongest CD62P fluorescence, followed by the 550°C annealed group and the unannealed group. Thus, it was shown that changes in the crystalline phase of TNT coatings on pure Ti surfaces have a positive impact on platelet adhesion and activation behavior.

It has also been shown that the application of APC on titanium surfaces can enhance osteogenic cell activity. The direct application of PRP on Ti6Al4V (rough, grit-blasted) was explored as a pretreatment step to enhance osteoblast attachment, proliferation, and extracellular matrix production.[16] PRP was obtained from supernatants of blood centrifuged at 150*g* for 10 min following leukocytes removal (mean platelet count: 800/nL to 1100/nL). A fourfold increase in platelet adhesion was reported on Ti surfaces when compared to tissue culture plates (control) and threefold capacity on Ti surface when PRP was added. Additionally, the number of cells was significantly higher (twofold increase – $^{*}p < 0.01$), on the PRP-supplemented titanium surfaces, as was ALP (fourfold) and calcium content (threefold). It was proposed that the complex fibrin network tightly connected with the cells may provide a natural three-dimensional niche in which adhesion, migration, and proliferation are facilitated. The interaction between the fibrin network and osteoblasts defines their fate and osteogenic capacity, especially in response to the growth factors PDGF-AA and transforming growth factor beta (TGF-β) that are commonly found in PRP. It was nevertheless acknowledging that the microenvironment included in this study does not recreate in vivo conditions and take into consideration the complex inflammatory response after biomaterial implantation.

Irastorza et al.[19] evaluated the osteogenic potential on either machined or surface-modified Ti6Al4V surfaces supplemented with plasma rich in growth factors (PRGF-liquid) or platelet-rich fibrin

(PRF-gel) using human dental pulp stem cells (hDPSCs). PRGF was produced by centrifugation of citrated human blood at 580*g* for 8 min at room temperature, activated by adding 10% calcium chloride and re-centrifuged at 3000*g* for 15 min/4°C. PRF was obtained by centrifugation at 580*g* for 8 min at room temperature. Fibrin clot membranes were used to supplement hDPSCs culture at 20% vol/vol, similar to previous reports. Both PRGF and PRF promoted hDPSCs osteogenic commitment, as measured by alkaline phosphate assay and alizarin red staining, especially on the modified surfaces. Gene expression of the bone markers Runt-related transcription factor 2 (RUNX2) (immature osteoblast) and secreted protein acidic and rich in cysteine (SPARC) (intermediate secretory osteoblast) was increased in the presence of PRGF and PRF, while the mature osteoblast marker transcription factor Sp7 (OSTERIX/SP7) was only enhanced in the presence of PRF. It was concluded that the treatment of modified Ti6Al4V alloy surfaces with PRF induced osteogenic lineage commitment of hDPSCs. Interestingly, a negative effect on osteoblast differentiation was observed when PRGF was used, which may be due to the presence of higher concentration of growth factors from soluble PRGF compared to insoluble PRF. This differential influence of platelet concentrates on cell function, including detrimental effects of high concentrations has also been reported in other studies.[21,22]

Taken together, the in vitro studies show that implant surface coating with APC generally results in positive outcomes in terms of surface modification and cell function, including enhanced osteogenic cell proliferation and differentiation.[16,19] Furthermore, the nature of the titanium implant surface can significantly impact on the fibrin network and platelet adhesion and activation upon exposure to APC. However, given the heterogeneity of the in vitro studies, in terms of different APC preparation protocol, implant surfaces, cell types, and experimental design, it is difficult to make specific conclusions on the ideal surface–APC combinations for enhanced osseointegration. Further exploration of the interaction of implant surfaces and APC is required using standardized protocols, especially in terms of fibrin matrix structure and surface protein deposition. In terms of influence on cell function, rather than solely focus on osteoblasts, it would be interesting to explore cells that are involved in the earlier stages of wound healing, such as macrophages, endothelial cells, and mesenchymal stem cells.

Notwithstanding the importance of in vitro studies to elucidate biological mechanisms, in vivo data are ultimately required to evaluate the clinically relevant influence of APC on osseointegration, and the next section explores the evidence from preclinical animal studies.

3 | PRECLINICAL ANIMAL STUDIES ON BENEFITS OF AN IMPLANT COATING WITH APCs

To answer the question whether APC influence titanium surfaces and bone formation in preclinical (animal) experiments, a literature review was performed in PubMed, Scopus, and Cochrane Library using the following MESH term parameters:

((((“Platelet-Rich Fibrin”[Mesh]) OR “Platelet-Rich Plasma”[Mesh]) AND “Osseointegration”[Mesh]) AND “Dental Implants”[Mesh])

From 2654 hits (excluding duplicates), a total of 12 studies (Table 2) were identified which reported on the effect of APC and included a control group with unassisted supplement (no APC). The references of the identified papers were screened for additional studies. Generally the studies exhibited significant heterogeneity, with a great variety of preclinical animal models, type of bone defects, and APC protocols, making it difficult to draw robust conclusions.

3.1 | Animal model and time frame used in studies

The literature search identifies 12 animal studies (Table 2) that investigated the effect of APC on osseointegration. Nine papers explored the use of PRP and three utilized L-PRF. Overall, the studies used a canine model (4/12), rat (4/12), rabbit (2/12), minipig (1/12), or goat (1/12). Mandibular alveolar bone defects, arguably the most applicable model to human translation, represented only 3/12 of the studies included.[26,29,34] The other 9/12 of studies used extraoral long bone such as femur, tibia, and radius. Experimental follow up was predominantly conducted at one time point (9/12), with a minority of studies (3/12) having more than one. Half of the studies included 12 weeks follow up, with the shortest time point being 2 weeks.[33]

3.2 | Studies utilizing PRP

Early studies utilizing PRP showed mixed outcomes on in vivo osseointegration. Weibrich et al.[24] inserted self-tapping Brånemark TiUnite implants bilaterally in distal femurs of 20 male New Zealand white rabbits, applying PRP in one of the 2 osteotomies. It was not possible to identify any statistically significant differences in bone–implant contact between the test and control groups. From studying the bone mineralization pattern using fluorochrome staining, it was noted that the impact of PRP might appear to be platelet concentration dependent, with a positive effect on bone regeneration seemingly achieved from a very limited range of approximately 1×10^6/µl. Similarly, the application of platelet-rich plasma (PRP) to trigger regeneration around implants (machined surface) in a dog jaw model did not show any benefits.[26] By using citrated blood, PRP was obtained by centrifugation at 1510 *g* for 10 min and subsequent activated by adding 10% calcium chloride (mean 1.5×10^6 platelets/µL). After 3 months, bone-to-implant contact (BIC) and bone area (BA) did not reveal any statistically significant differences for any of the parameters between PRP and the natural clot groups.

On the other hand, Fontana et al.[25] used a Wistar rats tibia model to compare the bone formation between titanium laminar implants with or without PRP, and observed significantly more newly formed bone in the PRP group than the control group. Similar results were also observed by Zechner et al.[23] when MK III Replace and MK III TiUnite implants were placed in mandibles of minipigs previously coated with PRP produced by double centrifugation of

TABLE 2 APC characteristics of the preclinical studies included (N/R not reported).

Study	Animal model	Follow up (weeks)	APC protocol	Anticoagulant	Outcomes
PRP					
Zechner et al.[23]	Minipig mandible	3, 6, 12	2890*g* for 6 m before surgery:153*g* for 12 min	Citrate phosphate dextrose	PRP was found to have a time- and site-dependent effect on peri-implant bone healing at 6 (control = 24.2% vs. PRP = 44.2%; $p = 0.013$) and 12 weeks (control = 51.3% vs. PRP = 44.2%; $p = 0.251$).
Weibrich et al.[24]	Rat femur	4	L-PRP: 1-3000 rpm × 3.75 m; 2–3000 rpm × 13 m	Citrate – dextrose solution	No differences in BIC between test and control at 28 days.
Fontana et al.[25]	Rat tibia	4	N/R	N/R	Newly formed bone in Ti/PRP group (30 ± 7 cm) was significantly greater than in Ti group (16 ± 3 cm) ($p = 0.05$).
Casati et al.[26]	Dog mandible	12	200 rpm for 10 min	3.2% Sodium citrate	BIC (control: 9.8 ± 13.7% vs. PRP: 9 ± 18.9%) and bone density (control:34 ± 23.3% vs. PRP: 32.5 ± 28.8%) did not showed significant difference ($p > 0.05$).
Nikolidakis et al.[27,28]	Goat femur	6	1–300*g*/5 m; 2–700*g*/15	3.2% Sodium citrate. Activation 10% calcium chloride +300 IU of bovine thrombin	PRP did not have any effect on cortical or trabecular bone response to Ca-P-coated implants. PRP in a liquid form increased early bone apposition to roughened Ti implants ($p < 0.05$)
Strechbein et al.[29]	Dog mandible	6, 12	L-PRP: 1-3000 *g* × 3.75 m; 2–3000 *g* × 13 m	Adenosine-citrate-dextrose-acid (ACD-A)	No significant difference between groups neither at 6 weeks (all $p \geq 0.06$) nor 12 weeks (all $p \geq 0.06$).
Jiang et al.[30]	Rat femur	12	Automated MCS® blood cell-separation system	3.2% Sodium citrate	PRP + TiO_2-nanosurface can improve healing at 12 weeks (BIC: control 12.1% vs. PRP + TiO_2-nano 79.7%) ($p < 0.05$)
Sun et al.[31]	Rat tibia	12	Automated MCS® blood cell-separation system	3.2% Sodium citrate	PRP + Ca-P-coated implants (BV/TV:47.8%) have shown beneficial effect on improving osseointegration compared to control (BV/TV:18.8%) ($p < 0.05$).
Kim et al.[32]	Rabbit tibia	4	N/R	N/R	In a contact osteogenesis model, rhBMP-2 significantly increased contact osteogenesis on implant surface, whereas PRP had no effect (mean BIC: 66.5 ± 14.1% vs. 16.4 ± 16%, $p = 0.004$).
L-PRF					
Oncu et al.[33]	Rabbit tibia	2, 4	2700 rpm for 12 m (L-PRF)	None (fresh blood)	BIC was enhanced when the surface was prewetted with L-PRF (52.6 ± 21.7% vs. 36.0 ±23.2% at third week and 54.6 ± 5.2% vs. 39.0 ± 8.9% at fourth week) ($p < 0.01$).
Neiva et al.[34]	Dog mandible	6	2700 rpm for 12 min (L-PRF)	None (fresh blood)	Ossean surface + L-PRF resulted in significantly higher BAFO level relative to its no L-PRF counterparts and double-etched surface with and without L-PRF ($p = 0.012$).
Benalcazar et al.[35]	Dog radius	12	2700 rpm for 12 min (L-PRF)	None (fresh blood)	L-PRF + wide osteotomies, prior to implantation, increased early bone formation compared to unfilled wide osteotomies (3 weeks $p < 0.03$). Not significant at 6 or 12 weeks ($p > 0.05$).

Abbreviations: BAFO, bone area fraction occupancy; BIC, bone implant contact; BV/TV, bone volume fraction; Ca-P, calcium phosphate; IU, international units; L-PRF, leukocyte platelet -rich fibrin; L-PRP, leukocyte platelet -rich plasma; N/R, not reported; PRP, platelet- rich plasma; rhBMP-2, recombinant human bone morphogenetic protein-2; Ti/PRP, titanium and platelet- rich plasma; TiO_2-nano, titanium dioxide nano.

citrated blood (2890*g* for 6 min and 153*g* for 12 min). During the early healing phase (6 weeks), superior performance was observed with the PRP group (control = 24.2% vs. PRP = 44.21%; $^*p = 0.013$). No statistically significant differences were observed after 12 weeks postimplantation (control = 51.3% vs. PRP = 44.2%; $p = 0.251$). Based also on previous reports,[36] the authors speculated that PRP contains physiological doses of naturally occurring TGF and PDGF growth factors that enhance angiogenesis and mitogenesis of mesenchymal stem cells (MSCs) precursors, which subsequently differentiate into osteoblasts during the early stages of healing.

The majority of more recent studies have failed to demonstrate a positive influence of PRP on osseointegration. Streckbein et al.[29] examined the benefits of combining PRP with different implant surfaces (Brånemark MK III, Osseotite, Xive, and Compress) inserted in each hemimandible of 12 female beagle dogs. No statistically significant differences were seen between the PRP and non-PRP group with respect to peri-implant bone remodeling and the resulting bone–implant contact rates, either after 6 or 12 weeks. Similar results were observed by Kim et al.,[32] where platelet-rich plasma alone was unable to trigger contact osteogenesis (osseointegration) on sand-blasted and acid-etched (SLA) surfaces. Implants were inserted in rabbit tibiae within "titanium tubes" and were supplemented with either PRP or recombinant human bone morphogenetic protein-2 (rhBMP-2). The titanium tubes served a dual purpose aimed at specifically evaluating contact osteogenesis. First, they precluded the involvement of the resident bone in the bone healing process, thus impeding distance osteogenesis, and allowing for the study of contact osteogenesis only (Figure 3). Second, they constrained the blood perfusion flowing to the implant surface by permitting circulation solely from the peripheral margins of the prepared osteotomy (openings of the tubes at the base of the cortical bone). Samples were retrieved after 4 weeks and analyzed by histomorphometry, including bone-to-implant contact (BIC) and bone area (BA). The use of rhBMP-2 was shown to induce statistically significant enhancement of contact osteogenesis on the implant surface compared to the PRP group (mean BIC: 66.53 ± 14.06% vs. 16.34 ± 15.98%, $^*p = 0.004$). Thus, this interesting model designed to evaluate the formation of contact osteogenesis failed to demonstrate a positive effect of PRP.

PRP effectiveness may be affected by implant surface characteristics. PRP was tested for its influence on the early bone healing around Ti implants, with and without calcium phosphate (CaP) coating installed, in goat femurs.[27,28] PRP fractions of either gel or liquid were applied onto sand-blasted/acid-etched Ti surfaces. Half of the samples were additionally treated with a thin Ca-P coating. The PRP protocol was described as "longer centrifugation time and lower gravitational force" leading to a mean platelet yield recovery of 1000×10^6/mL. PRP gelation was triggered by adding 10% calcium chloride solution and 300 IU of bovine thrombin before implant placement. Six weeks post implantation, the groups including PRP failed to provide a beneficial influence on bone formation around implants, as measured by BIC, BA, and endosteal bone formations length (EBFL), when compared to the control. However, the authors reported that the liquid version of PRP seemed to be slightly beneficial when applied to roughened titanium implants (implants without Ca-P coating) during the early postimplantation healing phase.

The use of PRP has been explored in compromised conditions. In this context, cryoprecipitate PRP has demonstrated synergy with different titanium surfaces (anodized, nanoporous, and plain TiO_2) and enhances the implant stability in osteoporotic bone of rat femurs.[30] Twelve weeks postimplantation, the combination of nanoporous TiO_2 with PRP treatment demonstrated statistically significantly superior performance, as measured by histomorphometry, μ-CT scan, and biomechanical evaluation. These results were subsequently validated by gene expression analysis showing increased expression of osteoprotegerin (OPG) and decreased levels of receptor activator of NF-κB ligand (RANKL) for the nanoporous surface–PRP combination. Downregulation of osteoclastogenesis through the RANKL-OPG pathway was therefore proposed as the biological mechanism for the improved osseointegration, alongside increased expression of the osteogenesis associated genes RUNX-2 and collagen type I alpha 1 (COL1A1). Similarly, the same osteoporosis model was used by Sun and co-workers (2020)[31] to test the ability of Ca-P coating supplemented with cryoprecipitate PRP on Ti implants to enhance osseointegration in tibias of rats. Twelve weeks postimplantation, statistically significant superiority was observed for the Ca-P + PRP group after μCT analysis, biomechanical testing, and histomorphometric evaluation. The authors concluded that the combination of Ca-P and PRP had an osteoinductive effect under osteoporotic conditions. It was therefore suggested that this approach enhanced the connection between the bone and the implant interface and hence may hold promise as a beneficial clinical method in patients with osteoporosis.

3.3 | Studies utilizing L-PRF

The three animal studies utilizing L-PRF all reported a positive outcome on osseointegration outcomes, such as bone–implant contact, especially at early time points. A histological study in rabbit tibias[33] illustrated that when the implant surface was prewetted with L-PRF exudate and an L-PRF membrane was inserted into the osteotomy prior to implant placement, significantly more new bone formation (32% vs. 12% at week 3, and 40% vs. 26% at week 4) could be obtained, when compared to unassisted healing. Also, the bone-to-implant contact was significantly higher in the L-PRF group (53% vs. 36% at week 3 and 55% vs. 39% at week 4).

Neiva et al.[34] inserted implants in dogs, immediately after extraction of their first mandibular molars. The entire gap between implant and surrounding bony socket wall (>2 mm in width) was either filled with L-PRF membranes, or with blood only. After 6 weeks of submerged healing, specimen were obtained for histological evaluation. The absence of L-PRF around implants often resulted in partial apical migration of the soft tissue into the gap (implant–bony walls), while this was not observed in the presence of L-PRF. The presence of L-PRF also resulted in a higher bone-to-implant contact area, and often the entire gap was filled with well-vascularized healthy bone.

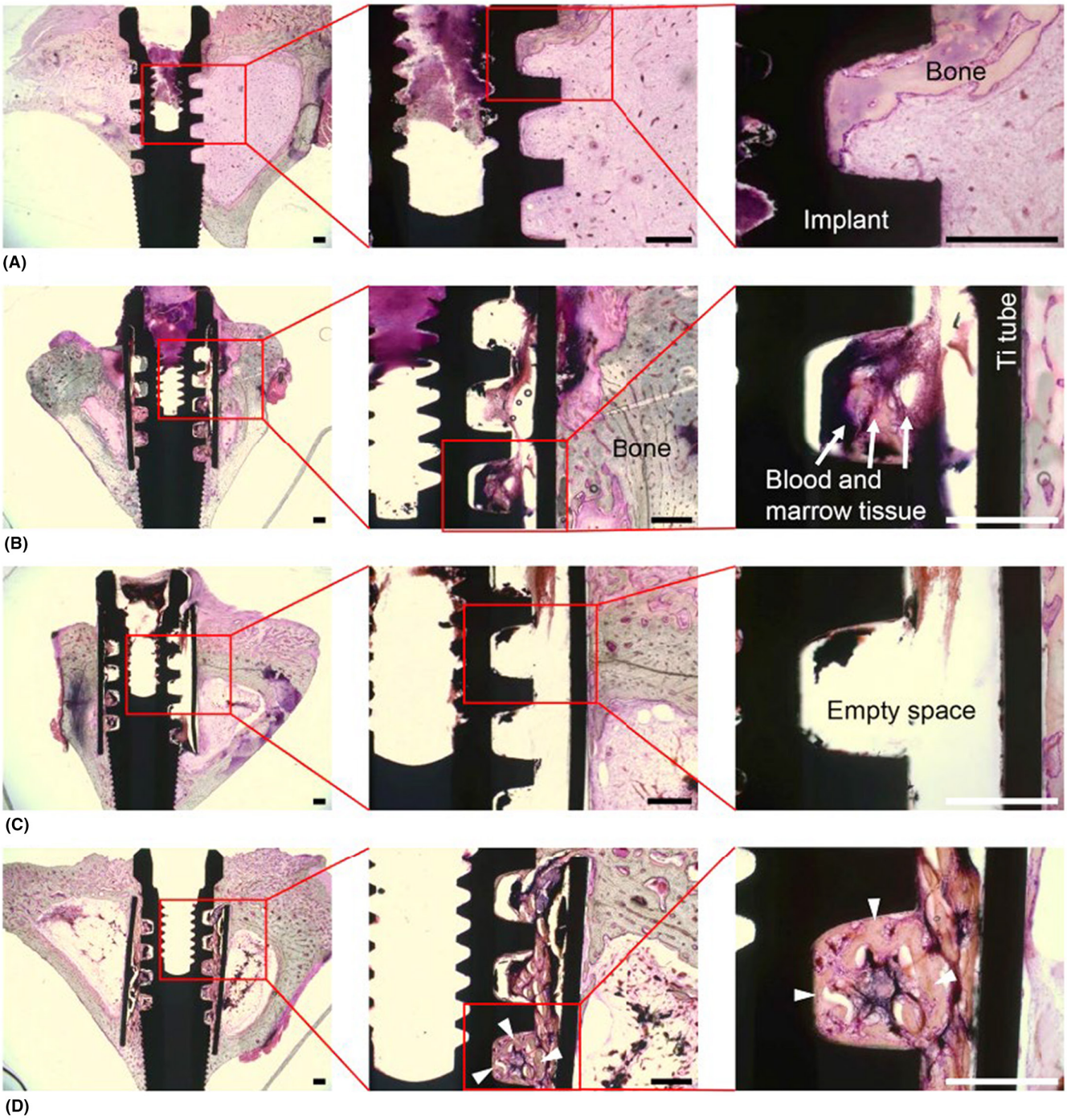

FIGURE 3 H&E staining of bone formation in the experiment to evaluate the influence of substances from blood and bone. (A) In the implant-only group, normal bone formation was observed around the SLA Ti implants. (B) In the Ti tube + implant group, there were many areas between the implant threads with no bone formation. (C) In the Ti tube + implant + PRP group, no bone formation was observed between many of the implant threads despite the PRP injection. (D) In the Ti tube + implant + rhBMP-2 group, bone formation (white arrowheads) was clearly observed. Scale bars = 500 μm (from Kim et al.[32]).

Benalcazar et al.[35] investigated the benefits of using L-PRF to enhance osseointegration around dental implants by using both conventional and wide osteotomies in a canine model (radius bone). L-PRF membranes were produced by centrifugation at 2700 rpm (408*g* force) for 12 min. After 3, 6, and 12 weeks, bone-to-implant contact (BIC) and bone area fraction occupancy (BAFO) were determined by histomorphometric analysis. BIC and BAFO demonstrated superior values for both variables at 3 weeks between wide osteotomies treated with L-PRF (~38% and ~56% for BIC and BAFO, respectively) and regular osteotomy without L-PRF supplement (~20% for both BIC and BAFO) (*$p < 00.03$). L-PRF-coated implants demonstrated superior bone formation compared to wide osteotomies after 3 weeks.

3.4 | Summary of animal studies

As a result of the great variety in protocols, combination of biomaterials, and clinical/therapeutic applications, comparison between the performances of different APC is challenging. This is mainly due to the empirical origins of the APC (predominantly PRP) and the numerous subsequent modifications to the method of preparation, mainly in centrifugation speed and rotor distance, type of equipment, and duration of centrifugation. Beyond these parameters, there is a great variety of critical factors to be considered such as type of blood collection tube, the use of anticoagulant reagents or activators, and the recipient site. Future research approaches need to evaluate the type of protein or groups of proteins in direct contact with the Ti surface that will establish the first line of reaction between biomaterials and inflammatory reaction once biomedical devices are implanted. This may provide a more comprehensive understanding of the blood plasma components – beyond the platelet and fibrin mesh role – and their interaction with different Ti surfaces.

In the context of a Ti osseointegration supplemented with APC, the formation of the unique interphase at the implant surface is also likely to significantly influence the healing capacity. Interestingly, the APC protocol not only modify the protein content and its resulting adsorption on the biomaterial surface, but also the characteristics of the fibrin network that will eventually determine how cells attach and produce extracellular matrix onto the Ti surface. The distinct APC-dependent protein interphase formed on the Ti surface before implantation opens new opportunities for controlling the early osteogenic events and subsequent osseointegration. This biomaterial surface modification can be considered to constitute a form of "clot tissue engineering,"[37] whereby the APC is utilized as a point-of-care approach to control the interphase between the surface of an implantable device (i.e., Ti dental implants) and the recipient for enhanced integration.

The development of these hemoderivatives has been mostly based on empirical methods whereby clinical handling and ease of implantation were the essential parameters, while their biological composition was largely overlooked. As a result, many contradictory results have been reported, which may be attributed to the lack of manufacturing standardization and the inherent patient-to-patient variation of the commencing material (autologous blood).[38] Therefore, while the possible benefits of APC in promoting the regeneration and reconstruction of orofacial tissues through biomaterial modification should be acknowledged,[7,8] the role of APC in osseointegration remains to be elucidated. The next section explores the evidence of the use of APC to promote osseointegration in clinical trials.

4 | CLINICAL STUDIES ON BENEFITS OF AN IMPLANT COATING WITH APCs

To answer the question whether APC can improve implant stability and reduce marginal bone loss, a literature review was performed with the following search terms: *platelet concentrates/PRP/PRGF/PRF and osseointegration*, *platelet concentrates/PRP/PRGF/PRF and biomimetics*, *platelet concentrates/PRP/PRGF/PRF and implant stability*, and *platelet concentrates/PRP/PRGF/PRF and ISQ*. Moreover, the references of the identified papers were screened for additional studies.

Only clinical studies RCTs or CCTs were considered and a control group with unassisted healing was a requirement. A total of 16 studies (Table 3) met the inclusion criteria. The majority of studies applied L-PRF (solid/liquid, $n = 13$), some PRP ($n = 3$), and none PRGF.

A large variety of applications (implant dipping in liquid, membrane over surgical site before wound closure, APC matrix in osteotomy) as well as indications (immediate [filling the jumping gap], early/late implant placement, immediate/early/late implant loading) have been used, besides a large diversity of implant brands, which makes the establishment of final evidence-based statements difficult.

4.1 | Implant stability

Thirteen studies reported on the effect/benefit of APC on the early implant stability (compared to unassisted healing).

4.1.1 | PRP

A short-term pilot study was conducted to investigate the effect of PRP on the implant stability by using ISQ values following one-stage implant placement in the anterior edentulous mandible. The authors reported no statistical difference was found in the ISQ values between the control and test groups after 4 days of implant placement.[39] Another clinical trial aimed to study the effect of PRP on the outcome of early loaded implants in the posterior maxilla. No additional benefit in the mean ISQ values between the control and test groups was found over 36 months of observation periods.[40] There were several limitations of the study such as relatively small sample size and variation in the observational periods. In summary, within the limits of the clinical trials, those studies demonstrated that the application of PRP at the time of implant placement do not offer additional clinical benefits for implant stability and osseointegration.

4.1.2 | L-PRF

Clinical effects of L-PRF in osseointegration were investigated in immediate implant placement protocol.[45,49] Öncü et al.[49] demonstrated a statistically significant difference in the means of ISQ values between the control and test groups at weeks 1 and 4 healing periods, however the difference was no longer found after 3 months of healing. The authors concluded that L-PRF application could promote implant stability at the early healing periods. On the contrary, in another clinical trial, an L-PRF membrane was directly applied to the peri-implant region (large distance) following immediate implant placement in the maxilla, showing no significant effect on implant stability (ISQ) values between the groups throughout the healing

TABLE 3 Clinical randomized controlled trials (RCTs) and controlled clinical trials (CCTs) exploring the benefits of using APCs for the improvement of the osseointegration process.

Article	Study type	Subjects (*n*) treated area gender age	Implant site info loading approach implant brand implant surface	Centrifuge RPM/ minutes	Outcome C = control (*n*) *T* = test (*n*)	Conclusion
A. PRP						
Monov et al.[39]	RCT *split-mouth*	*n* = 10 LJ ♀ = 6/♂ = 4 Age: 53–80 years	Healed sites Immediate abutment Nobel Biocare	Monovette syst 2400 rpm, 10 min 3600 rpm, 10 min	*RAF* C: blood clot only (10) *T*: PRP liquid $^{dip+inj}$ (10)	*Addition of PRP* (*up to 44 d*) *gave*: =RFA values
Ergun et al.[40]	CCT *split-mouth*	*n* = 32 UJ post. ♀ = 13/♂ = 18 Age: 44 ± 13 years	Healed sites Early loading (7 days) Straumann	Curasan PRP kit 2400 rpm, 10 min 3600 rpm, 10 min	*ISQ* C: blood clot only (32) *T*: PRP liquid$^{dip\ 3-5'+inj}$ (32)	***Addition of PRP gave*:** **>ISQ at ins (C: 72 ± 9, *T*: 75 ± 6),** =ISQ at 1 year (C: 75 ± 9, *T*: 75 ± 9), =ISQ at 3 years (C: 75 ± 7, *T*: 74 ± 8)
Khan et al.[41]	RCT *split-mouth*	*n* = 12 UJ&LJ ♀/♂ NR Age: NR	Immediate placement Delayed loading (12 weeks) DIO UFII implant	NR 5800 rpm, 8 min 2400 rpm, 5 min	*MBL*, *bone density* C: blood clot only to fill gap (6) *T*: PRP liquid ^{inj} (6)	*Addition of PRP* (*up to 26 w load.*) *gave*: = MBL change (C: −0.4 ± 0.8, *T*: −0.1 ± 0.1 mm), =bone mineral density (CBCT)
B. PRGF						
C. L-PRF						
Öncü et al.[33]	RCT *split-mouth*	*n* = 20 UJ&LJ ♀ = 6/♂ = 14 Age: 44 ± 13 years	Healed site Immediate healing cap Ankylos	PC-02 Process 2700 rpm, 12 min	*ISQ* C: blood clot (33) *T*1: L-PRF exudate ^{dip} +1 L-PRF membr ^{ins} (31)	***Addition of L-PRF gave*:** =ISQ at ins (C: 63 ± 14, *T*: 59 ± 16), **>ISQ at 1w (C: 60 ± 12, *T*: 69 ± 11),** **>ISQ at 4w (C: 71 ± 8, *T*: 77 ± 7)**
Boora et al.[42]	RCT *parallel*	*n* = 20 UJ ant. ♀ = 5/♂ = 15 Age: 18–33 years	Healed site Immediate nonfunctional provisionalization Adin Dental	R-8C Remi 3200 rpm, 12 min	*MBL* C: blood clot (10) *T*: 1-L-PRF membr $^{cover\ bone}$ (10)	***Addition of L-PRF gave*:** **<MBL changes (0–3 m),** **(C: −0.7 ± 0.3, *T*: −0.3 ± 0.1 mm),** =PPD
Pirpir et al.[43]	RCT *split-mouth*	*n* = 12 UJ ant. ♀ = 5/♂ = 7 Age: 20–68 years	Healed sites Immediate gingival former Bego Semados	Medifuge 2700 rpm, 4 min, 2400 rpm, 4 min, 2700 rpm, 4 min, 3000 rpm, 3 min	*ISQ* C: blood clot (20) T: CGF exudate ^{irr} +1 CGF membr ^{ins} (20)	***Addition of L-PRF gave*:** =ISQ at ins (C: 76 ± 6, *T*: 78 ± 3), **>ISQ at 1 w (C: 74 ± 5, *T*: 79 ± 3),** **>ISQ at 4 w (C: 73 ± 6, *T*: 79 ± 3)**
Khan et al.[44]	RCT *split-mouth*	*n* = 17 UJ&LJ ♀ = 9/♂ = 8 Age: 33 ± 2 years	Imm. plac., JG < 2 mm Delayed loading (4–5 m) Myriad plus	Remi 3000 rpm, 12 min	*MBL* C: blood clot only to fill gap (14) *T*: L-PRF exudate ^{dip} +1 L-PRF membr ^{ins} (14)	*Addition of L-PRF gave* (*up to 9 m*): =MBL changes (C: −1.2, *T*: −0.8 mm), =PPD
Diana et al.[45a]	RCT *parallel*	*n* = 31 UJ&LJ ♀ = 13/♂ = 18 Age: 20–46 years	Imm. plac., JG = large Delayed loading (3 m) Osstem TS	NR	*ISQ*, *MBL* C: blood clot only to fill gap (20) *T*: 1 L-PRF membr ^{ins} (21)	*Addition of L-PRF gave*: =ISQ at ins (C: 61 ± 11, *T*: 57 ± 19), =ISQ at 3 m (C: 70 ± 9, *T*: 71 ± 8), =MBL changes (C: + 0.9, *T* + 1.2 mm) =PPD

(Continues)

TABLE 3 (Continued)

Article	Study type	Subjects (*n*) treated area gender age	Implant site info loading approach implant brand implant surface	Centrifuge RPM/ minutes	Outcome C = control (*n*) *T* = test (*n*)	Conclusion
Tabrizi et al.[46]	RCT *split-mouth*	*n* = 20 UJ post. ♀ = 11/♂ = 9 Age: 40 ± 7 years	Healed sites Immediate abutment BEGO	IntraSpin 2800 rpm, 12 min	*ISQ* C: blood clot only (20) *T*: 1 L-PRF membr ^{ins} (20)	***Addition of L-PRF gave*:** **>ISQ at 2 w (C: 58 ± 4, *T*: 61 ± 3),** **>ISQ at 4 w (C: 67 ± 4, *T*: 70 ± 3),** **>ISQ at 6 w (C: 76 ± 3, *T*: 78 ± 3)**
Torkzaban et al.[47]	CCT *split-mouth*	*n* = 10 UJ&LJ ♀ = 5/♂ = 5 Age: 26–60 years	Healed sites Immediate abutment Dio Busan	Froilabo velocity 2000 rpm, 10 min	*ISQ* C: blood clot only (25) T: L-PRF exudate ^{dip} +1 L-PRF membr ^{ins} (25)	***Addition of L-PRF gave*:** =ISQ at ins (C: 58 ± 4, *T*: 60 ± 5), **>ISQ at 1 w (C: 56 ± 4, *T*: 60 ± 5),** **>ISQ at 4 w (C: 63 ± 5, *T*: 67 ± 5)**
Alhussaini[48b]	CCT *parallel*	*n* = 17 UJ&LJ ♀ = 10/♂ = 7 Age: 25–66 years	Healed site Delayed loading (… w) Implantium	NR 3200 rpm, 12 min	*ISQ* C: blood clot (51) *T*: 1 L-PRF membr ^{ins} (17)	*Addition of L-PRF gave*: =ISQ at ins (C: 71 ± 8, *T*: 73 ± 8), =ISQ at 6 w (C: 67 ± 8, *T*: 71 ± 7), =ISQ at 12 w (C: 71 ± 8, *T*: 75 ± 8)
Öncü et al.[49]	RCT *split-mouth*	*n* = 26 UJ&LJ post. ♀ = 10/♂ = 16 Age: 40 ± 12 years	Imm. plac., JG = 1 mm Delayed loading (3 m) Straumann	PC-02 process 2700 rpm, 12 min	*ISQ*, *MBL* C: blood clot only to fill gap (30) *T*: L-PRF membr ^{ins} (30)	***Addition of L-PRF gave*:** =ISQ at ins (C: 25 ± 12, *T*: 26 ± 13), **>ISQ at 1w (C: 49 ± 14, *T*: 54 ± 16),** **>ISQ at 4w (C: 61 ± 12, *T*: 70 ± 12),** =ISQ at 12w (C: 70 ± 11, *T*: 71 ± 10), **<MBL change at 1st year** **(C: −1.3 ± 0.6, *T*:−0.7 ± 0.5)**
Özveri-Koyuncu et al.[50]	CCT *split-mouth*	*n* = 12 LJ ant. ♀ = 7/♂ = 5 Age: 53 ± 86 years	Healed sites Immediate abutment Biomet 3i	Medifuge 2700 rpm, 2 min, 2400 rpm, 4 min, 2700 rpm, 4 min, 3000 rpm, 3 min	*ISQ* C: blood clot (12) *T*: 1 CGF membr ^{ins} (12)	*Addition of L-PRF gave*: =ISQ at ins (C: 62 ± 8, *T*: 68 ± 10), =ISQ at 1 weeks (C: 63 ± 6, *T*: 64 ± 10), =ISQ at 2 weeks (C: 62 ± 7, *T*: 63 ± 9), =ISQ at 4 week (C: 65 ± 5, *T*: 67 ± 5)
Güvenç et al.[51]	RCT *parallel*	*n* = 15 LJ ♀ = …/♂ = … age: 25–67 years	Healed sites Immediate gingival former Bego Semados	Process 700 rpm, 3 min	*ISQ* C: blood clot (12) *T*: i-PRF liquid $^{irr+inj}$ (12)	*Addition of L-PRF gave*: =ISQ at ins (C: 72 ± 9, *T*: 72 ± 9), =ISQ at 1 week (C: 72 ± 10, *T*: 74 ± 8), =ISQ at 2 weeks (C: 72 ± 8, *T*: 75 ± 8), =ISQ at 4 weeks (C: 73 ± 8, *T*: 77 ± 5)
Fernandes et al.[52]	RCT *split-mouth*	*n* = 15 UJ&LJ post. ♀ = 23/♂ = 13 Age: 18–improving osseointegration compared to control65 years	Healed sites Delayed loading (2 m) NR	NR 2000 rpm, 10 min RCF: 268	*ISQ*, *MBL* C: blood clot (15) *T*: a-cellular plasma $^{irr+inj}$ (12)	*Addition of PRF/CGF gave*: =ISQ changes =radiodensity changes =horizontal/vertical bone gap changes

periods.[45] It is noteworthy that those results from the two clinical trials cannot be directly compared due to several variations in methodology: different locations of implant placement (posterior vs. anterior dentition), L-PRF production protocol and application approaches (socket coating vs. direct application), implant surface characteristics and designs.

The remaining nine clinical studies investigated the effects of L-PRF on implant placement at healed sites. Different L-PRF products according to various L-PRF production protocols were tested on implant stability. In two clinical trials, a liquid form of L-PRF products was directly applied to implant surfaces before the placement, demonstrating no significant difference between the coated and noncoated groups.[51,52] Other clinical trials used different L-PRF application protocols to ascertain any additional clinical benefits. An L-PRF membrane was inserted into the prepared osteotomy site prior to implant placement in several studies,[42,46,48,50] or a combination approach of membrane insertion and direct application of L-PRF exudates onto the implant surface was used in the other studies.[43,44,47,53] Regardless of the different L-PRF membrane application approaches, some of the studies demonstrated initial positive effects of L-PRF on osseointegration by showing higher ISQ values at the early healing periods.[43,46,47,53] However, at week 12 or later, this initial improvement of implant stability dissipated, and no clinical significance was noted at the long-term observation. On the contrary, the other studies failed to show any difference in the mean ISQ values between the L-PRF and control groups even at the early time point.[48,50] Therefore, it can be summarized that there is no clear additional benefit of L-PRF use in immediate and delayed implant placement protocol. It is important to note that there were several limitations in the aforementioned studies such as small study power, lack of standardization of the peri-implant region dimensions, different implant systems, and L-PRF preparation protocols (rpm and time), thus it is difficult to compare the results directly and draw a robust conclusion from the studies.

4.2 | Marginal bone level

Six studies reported on the effect of platelet concentrates on the peri-implant bone changes (again compared to unassisted healing).

4.2.1 | PRP

Khan et al.[41] investigated the effects of local injection of PRP on marginal bone loss and bone density around immediate implant placement over 6 months of observational period, demonstrating no statistically significant differences in the crestal bone level and bone density changes between the control and test groups. There were a number of limitations with the study, including small sample size (six cases per group), lack of each edentulous site information, short follow-up period, and no standardized depth of implant placement protocol. Within the limitations of the study,

TABLE 3 (Continued)

Article	Study type	Subjects (*n*) treated area gender age	Implant site info loading approach implant brand implant surface	Centrifuge RPM/ minutes	Outcome C = control (*n*) *T* = test (*n*)	Conclusion
Kapoor et al.[53]	RCT *split-mouth*	*n* = 21 UJ&LJ ♀ = 10/♂ = 11 Age: 23–70 years	Healed sites NR Nobel Replace	IntraSpin 3000 rpm, 10 min	*ISQ* C: blood clot (30) *T*: L-PRF exudate ^{dip} +1 L-PRF membr ^{ins} (30)	***Addition of L-PRF gave:*** =ISQ at ins (C: 25 ± 3, *T*: 25 ± 1), **>ISQ at 1w (C: 47 ± 6, *T*: 50 ± 5),** **>ISQ at 1 m (C: 57 ± 4, *T*: 60 ± 5),** =ISQ at 3 m (C: 70 ± 4, *T*: 68 ± 6)

Note: Data in bold reached statistical significance. Different applications, $^{cover\ bone}$ = covering bone around implant, ^{ins} = inserted in osteotomy before implant insertion, ^{inj} = injected in osteotomy before implant insertion, ^{dip} = dipping implant into liquid, ^{irr} = irrigating/humidification implant surface. Different outcome variables, MBL, marginal bone level (+=bone gain, − is bone loss); PPD, probing pocket depth; ISQ, implant stability quotient (Ostell); RAF, resonance frequency analysis (with transducer).

Abbreviations: ant, anterior; CGF, concentrated growth factor; Imm. plac, immediate implant placement; i-PRF, injectable PRF; JG, jumping gap; LJ, lower jaw; L-PRF, leucocyte- and platelet-rich fibrin; min, minutes; post., posterior; PRGF, plasma-rich in growth factors; PRP, platelet-rich plasma; RCF, relative centrifugal force; rpm, revolutions per minute; UJ, upper jaw.

[a]Patients: mix split-mouth/parallel concept.

[b]Different arms, unclear data comparison.

the authors concluded that local application of liquid form of PRP following immediate implant placement did not result in any decrease in marginal bone loss.

4.2.2 | L-PRF

Three clinical trials[44,45,49] applied L-PRF membranes in the peri-implant regions (jumping gaps) directly following immediate implant placement. Although all three studies showed a tendency of minor marginal bone-level changes in the L-PRF groups compared to the control groups, only in one study this difference reached a statistical significance.[49] The mean marginal bone resorption was higher at 12 months in the control group (control group 1.3 ± 0.6 mm vs. L-PRF group 0.7 ± 0.5 mm), which reached a statistically significant difference. However, it is interesting to note that this difference was not translated into the mean gingival recession values at 12 months (control group 0.51 mm vs. L-PRF group 0.49 mm).[49]

In another clinical trial, Boora et al.[42] reported a reduction in the marginal bone height changes in the L-PRF group at 3 months and it was statistically significant. However, a cautious interpretation of the findings is required as the mean difference was less than 0.5 mm between the groups from the radiological analysis, and no detailed information on the standardization of radiological technique was reported. In addition, insufficient information on the implant dimensions and edentulous sites profile was provided.

More recently, in a double blinded split-mouth RCT, de Oliveira Fernandes et al.[52] investigated the effect of liquid PRF-coated implant surface on osseointegration, survival rate, and marginal bone loss up after 1 year. No statistically significant difference was found in any parameters between the control and PRF-coated groups.

Arakeeb et al.[54] examined the benefits of placing small pieces of L-PRF clots in the osteotomy by evaluating CBCT-assisted relative bone density (RBD) at 6 and 12 weeks. The authors demonstrated that the application of L-PRF resulted in an increase in the relative bone density compared to the control group at both time points. However, it is important to realize that this new measuring technique has not been validated due to numerous technical difficulties associated with CBCT images such as beam hardenings around implant fixtures.

4.3 | Peri-implant soft tissues

Platelet concentrates have also been assessed for their ability to promote peri-implant soft tissue healing. A split mouth RCT involving 20 fully edentulous patients found no statistically significant differences in probing depths around PRP-treated and control implants up to 12 months follow up.[55] Similarly, several other studies have also reported no statistically significant changes in probing depths following the application of L-PRF.[42,44,45] However, a pilot clinical trial showed that the application of an L-PRF membrane can increase the width of keratinized mucosa around implants.[56] Furthermore, a recent RCT showed that L-PRF membranes enhance peri-implant tissue wound healing, with gains in soft tissue width and thickness around nonsubmerged implants.[57] Therefore, the potential of L-PRF membranes to enhance peri-implant soft tissue healing warrants further investigation.

4.4 | Summary of clinical studies

Clinical benefits of PRP and liquid form of L-PRF application to any implant surface seem limited to none in terms of implant stability and marginal bone loss. The application of L-PRF membranes in the osteotomy site, however, may produce positive clinical effects at the early stage of healing (up to 4–6 weeks) by promoting early implant stability and reducing marginal bone loss. These conclusions are in accordance with recent systematic reviews.[10,58] However, such effects were short lived in those clinical trials and careful interpretation and cautious conclusion should be drawn as there were various limitations in methodology of the studies discussed earlier. One of the main concerns was that there was no single standard preparation protocol for L-PRF products, making it difficult to compare the results due to variations in the concentration of leukocytes and other immune cells in the different L-PRF products.

5 | CONCLUSIONS AND FUTURE DIRECTIONS

There is a sound rationale for the use of APC to modify the implant surface to make it more biocompatible with the host and hence enhance the wound healing process leading to improved osseointegration. Indeed, in vitro laboratory studies consistently demonstrate that APC are able to enhance the osteogenic functions of osteoblasts and their precursors. However, based on the preclinical animal studies and clinical trials, there is limited evidence for a clinically relevant effect, especially for the use of PRP preparations. L-PRF appears to have some potential to enhance the early stages of wound healing, but this needs to be further explored. The available literature has significant limitations not only due to the inherent difficulties of utilizing autologous products, but also due to a lack of standardization of APC preparation methodologies as well as the protocols for clinical application of the products. It is also possible that the utilization of APC does not provide any further biological benefit beyond the natural healing response or any effect of APC is highly transient during the very early healing process and hence does not influence the bone formation progress.

Future studies should focus on better understanding the influence of APC preparation and application protocols on the interaction between proteins and implant surfaces and explore the in vitro effects on not only bone forming cells, but also other cell types that are critical during the early wound healing process, especially those associated with inflammation and angiogenesis. Standardization of

APC preparation and clinical application protocols is also important to support wider clinical implementation. Finally, in order to circumvent the variability that arises from autologous products, the use of "off-the-shelf" preparations could also be explored to assess the viability of the "biomimetics" approach for surface modification aimed at enhancing osseointegration.

ACKNOWLEDGMENT

Open access publishing facilitated by The University of Queensland, as part of the Wiley - The University of Queensland agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

All (co)-authors declare that they have no conflict of interest in relation to this paper, even though they might have received research support from different implant companies including Camlog, Dentsply Sirona, Straumann, Henry Schein, Giestlich, and Straumann.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

ORCID

Sašo Ivanovski https://orcid.org/0000-0001-5339-0936
Ryan S. B. Lee https://orcid.org/0000-0001-6041-4799
Marc Quirynen https://orcid.org/0000-0001-8253-3908

REFERENCES

1. Salvi GE, Bosshardt DD, Lang NP, et al. Temporal sequence of hard and soft tissue healing around titanium dental implants. *Periodontol*. 2015;68(1):135-152.
2. Berglundh T, Abrahamsson I, Lang NP, Lindhe J. De novo alveolar bone formation adjacent to endosseous implants. *Clin Oral Implants Res*. 2003;14(3):251-262.
3. Lang NP, Salvi GE, Huynh-Ba G, Ivanovski S, Donos N, Bosshardt DD. Early osseointegration to hydrophilic and hydrophobic implant surfaces in humans. *Clin Oral Implants Res*. 2011;22(4):349-356.
4. Ivanovski S, Hamlet S, Salvi GE, et al. Transcriptional profiling of osseointegration in humans. *Clin Oral Implants Res*. 2011;22(4):373-381.
5. Abrahamsson I, Berglundh T, Linder E, Lang NP, Lindhe J. Early bone formation adjacent to rough and turned endosseous implant surfaces. An experimental study in the dog. *Clin Oral Implants Res*. 2004;15(4):381-392.
6. Smeets R, Stadlinger B, Schwarz F, et al. Impact of dental implant surface modifications on osseointegration. *Biomed Res Int*. 2016;2016:6285620.
7. Anitua E, Tejero R, Alkhraisat MH, Orive G. Platelet-rich plasma to improve the bio-functionality of biomaterials. *BioDrugs*. 2013;27(2):97-111.
8. Simonpieri A, Del Corso M, Vervelle A, et al. Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part 2: bone graft, implant and reconstructive surgery. *Curr Pharm Biotechnol*. 2012;13(7):1231-1256.
9. Huang Y, Bornstein MM, Lambrichts I, Yu HY, Politis C, Jacobs R. Platelet-rich plasma for regeneration of neural feedback pathways around dental implants: a concise review and outlook on future possibilities. *Int J Oral Sci*. 2017;9(1):1-9.
10. Qu C, Luo F, Hong G, Wan Q. Effects of platelet concentrates on implant stability and marginal bone loss: a systematic review and meta-analysis. *BMC Oral Health*. 2021;21(1):579.
11. Dohan Ehrenfest DM, 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(3):158-167.
12. Visalakshan RM, MacGregor MN, Sasidharan S, et al. Biomaterial surface hydrophobicity-mediated serum protein adsorption and immune responses. *ACS Appl Mater Interfaces*. 2019;11(31):27615-27623.
13. Vroman L. The life of an artificial device in contact with blood: initial events and their effect on its final state. *Bull N Y Acad Med*. 1988;64(4):352-357.
14. Lu X, Xu P, Ding HM, Yu YS, Huo D, Ma YQ. Tailoring the component of protein corona via simple chemistry. *Nat Commun*. 2019;10(1):4520.
15. Sánchez-Ilárduya MB, Trouche E, Tejero R, Orive G, Reviakine I, Anitua E. Time-dependent release of growth factors from implant surfaces treated with plasma rich in growth factors. *J Biomed Mater Res A*. 2013;101(5):1478-1488.
16. Lee JH, Nam J, Nam KW, Kim HJ, Yoo JJ. Pre-treatment of titanium alloy with platelet-rich plasma enhances human osteoblast responses. *Tissue Eng Regen Med*. 2016;13(4):335-342.
17. Lollobrigida M, Maritato M, Bozzuto G, Formisano G, Molinari A, De Biase A. Biomimetic implant surface functionalization with liquid L-PRF products: In vitro study. *Biomed Res Int*. 2018;2018:9031435.
18. Zhang L, Liao X, Fok A, Ning C, Ng P, Wang Y. Effect of crystalline phase changes in titania (TiO_2) nanotube coatings on platelet adhesion and activation. *Mater Sci Eng C*. 2018;82:91-101.
19. Irastorza I, Luzuriaga J, Martinez-Conde R, Ibarretxe G, Unda F. Adhesion, integration and osteogenesis of human dental pulp stem cells on biomimetic implant surfaces combined with plasma derived products. *Eur Cell Mater*. 2019;38:201-214.
20. Andrade CX, Quirynen M, Rosenberg DR, Pinto NR. Interaction between different implant surfaces and liquid fibrinogen: a pilot in vitro experiment. *Biomed Res Int*. 2021;2021:9996071.
21. Creeper F, Lichanska AM, Marshall RI, Seymour GJ, Ivanovski S. The effect of platelet-rich plasma on osteoblast and periodontal ligament cell migration, proliferation and differentiation. *J Periodontal Res*. 2009;44(2):258-265.
22. Fernández-Medina T, Vaquette C, Ivanovski S. Systematic comparison of the effect of four clinical-grade platelet rich hemoderivatives on osteoblast behaviour. *Int J Mol Sci*. 2019;20(24):6243.
23. Zechner W, Tangl S, Tepper G, et al. Influence of platelet-rich plasma on osseous healing of dental implants: a histologic and histomorphometric study in minipigs. *Int J Oral Maxillofac Implants*. 2003;18(1):15-22.
24. Weibrich G, Hansen T, Kleis W, Buch R, Hitzler WE. Effect of platelet concentration in platelet-rich plasma on peri-implant bone regeneration. *Bone*. 2004;34(4):665-671.
25. Fontana S, Olmedo DG, Linares JA, Guglielmotti MB, Crosa ME. Effect of platelet-rich plasma on the peri-implant bone response: an experimental study. *Implant Dent*. 2004;13(1):73-78.
26. Casati MZ, de Vasconcelos Gurgel BC, Gonçalves PF, et al. Platelet-rich plasma does not improve bone regeneration around peri-implant bone defects—a pilot study in dogs. *Int J Oral Maxillofac Surg*. 2007;36(2):132-136.
27. Nikolidakis D, Van Den Dolder J, Wolke JGC, Jansen JA. Effect of platelet-rich plasma on the early bone formation around Ca-P-coated and non-coated oral implants in cortical bone. *Clin Oral Implants Res*. 2008;19(2):207-213.
28. Nikolidakis D, Van Den Dolder J, Wolke JGC, Stoelinga PJW, Jansen JA. The effect of platelet-rich plasma on the bone healing around

calcium phosphate-coated and non-coated oral implants in trabecular bone. *Tissue Eng*. 2006;12(9):2555-2563.
29. Streckbein P, Kleis W, Buch RS, Hansen T, Weibrich G. Bone healing with or without platelet-rich plasma around four different dental implant surfaces in beagle dogs. *Clin Implant Dent Relat Res*. 2014;16(4):479-486.
30. Jiang N, Du P, Qu W, Li L, Liu Z, Zhu S. The synergistic effect of TiO(2) nanoporous modification and platelet-rich plasma treatment on titanium-implant stability in ovariectomized rats. *Int J Nanomedicine*. 2016;11:4719-4733.
31. Sun P, Wang Y, Xu D, & Gong K. The Calcium Phosphate Modified Titanium Implant Combined With Platelet-Rich Plasma Treatment Promotes Implant Stabilization in an Osteoporotic Model. *J Craniofac Surg*. 2020;32(2):603-608.
32. Kim UG, Choi JY, Lee JB, Yeo IL. Platelet-rich plasma alone is unable to trigger contact osteogenesis on titanium implant surfaces. *Int J Implant Dent*. 2022;8(1):25.
33. Öncü E, Bayram B, Kantarci A, Gülsever S, Alaaddinoğlu EE. Positive effect of platelet rich fibrin on osseointegration. *Med Oral Patol Oral Cir Bucal*. 2016;21(5):e601-e607.
34. Neiva RF, Gil LF, Tovar N, et al. The synergistic effect of leukocyte platelet-rich fibrin and micrometer/nanometer surface texturing on bone healing around immediately placed implants: an experimental study in dogs. *Biomed Res Int*. 2016;2016:9507342.
35. Benalcázar Jalkh EB, Tovar N, Arbex L, et al. Effect of leukocyte-platelet-rich fibrin in bone healing around dental implants placed in conventional and wide osteotomy sites: a pre-clinical study. *J Biomed Mater Res B Appl Biomater*. 2022;110(12):2705-2713.
36. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: growth factor enhancement for bone grafts. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;85(6):638-646.
37. Fernandez-Medina T, Vaquette C, Gomez-Cerezo MN, Ivanovski S. Characterization of the protein corona of three chairside hemoderivatives on melt electrowritten polycaprolactone scaffolds. *Int J Mol Sci*. 2023;24(7):6162-6183.
38. Sánchez M, Anitua E, Azofra J, Andía I, Padilla S, Mujika I. Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. *Am J Sports Med*. 2007;35(2):245-251.
39. Monov G, Fuerst G, Tepper G, Watzak G, Zechner W, Watzek G. The effect of platelet-rich plasma upon implant stability measured by resonance frequency analysis in the lower anterior mandibles. *Clin Oral Implants Res*. 2005;16(4):461-465.
40. Ergun G, Egilmez F, Cekic-Nagas I, Karaca İR, Bozkaya S. Effect of platelet-rich plasma on the outcome of early loaded dental implants: a 3-year follow-up study. *J Oral Implantol*. 2013;39(s1):256-263.
41. Khan AS, Zaheer N, Zaigham AM, Shahbaz M, Zaheer U, Alam MK. Effect of platelet-rich plasma on bone healing in immediate implants analyzed by cone beam computerized tomography: a randomized controlled trial. *Biomed Res Int*. 2021;2021:6685991.
42. Boora P, Rathee M, Bhoria M. Effect of platelet rich fibrin (PRF) on peri-implant soft tissue and crestal bone in one-stage implant placement: a randomized controlled trial. *J Clin Diagn Res*. 2015;9(4):Zc18-Zc21.
43. Pirpir C, Yilmaz O, Candirli C, Balaban E. Evaluation of effectiveness of concentrated growth factor on osseointegration. *Int J Implant Dent*. 2017;3(1):7.
44. Khan ZA, Jhingran R, Bains VK, Madan R, Srivastava R, Rizvi I. Evaluation of peri-implant tissues around nanopore surface implants with or without platelet rich fibrin: a clinico-radiographic study. *Biomed Mater*. 2018;13(2):025002.
45. Diana C, Mohanty S, Chaudhary Z, Kumari S, Dabas J, Bodh R. Does platelet-rich fibrin have a role in osseointegration of immediate implants? A randomized, single-blind, controlled clinical trial. *Int J Oral Maxillofac Surg*. 2018;47(9):1178-1188.
46. Tabrizi R, Arabion H, Karagah T. Does platelet-rich fibrin increase the stability of implants in the posterior of the maxilla? A split-mouth randomized clinical trial. *Int J Oral Maxillofac Surg*. 2018;47(5):672-675.
47. Torkzaban P, Khoshhal M, Ghamari A, Tapak L, Houshyar E. Efficacy of application of platelet-rich fibrin for improvement of implant stability: a clinical trial. *J Long-Term Eff Med Implants*. 2018;28(4):259-266.
48. Alhussaini AHA. Effect of platelet-rich fibrin and bone morphogenetic protein on dental implant stability. *J Craniofac Surg*. 2019;30(5):1492-1496.
49. Öncü E, Erbeyoğlu AA. Enhancement of immediate implant stability and recovery using platelet-rich fibrin. *Int J Periodontics Restorative Dent*. 2019;39(2):e58-e63.
50. Özveri Koyuncu B, İçpınar Çelik K, Özden Yüce M, Günbay T, Çömlekoğlu ME. The role of concentrated growth factor on implant stability: a preliminary study. *J Stomatol Oral Maxillofac Surg*. 2020;121(4):363-367.
51. Güvenç S, Durmuşlar MC, Ballı U. The effects of injectable platelet-rich fibrin on implant stability. *Int J Oral Maxillofac Implants*. 2022;37(6):1145-1150.
52. de Oliveira Fernandes GV, Malta Santos NB, Correia de Sousa MF, Fernandes JCH. Liquid platelet-rich fibrin coating implant surface to enhance osseointegration: a double-blinded, randomized split-mouth trial with 1-year follow-up. *Int J Oral Maxillofac Implants*. 2022;37(1):159-170.
53. Kapoor A, Ali AR, Saini N, Gautam K, Goyal A, Prakash V. Comparative evaluation of implant stability with and without autologous platelet-rich fibrin prior to prosthetic loading – a split-mouth randomized clinical trial. *J Indian Soc Periodontol*. 2022;26(2):137-142.
54. Arakeeb MAA, Zaky AA, Harhash TA, Salem WS, El-Mofty M. Effect of combined application of growth factors and diode laser bio-stimulation on the osseo integration of dental implants. *Open Access Maced J Med Sci*. 2019;7(15):2520-2527.
55. Vishnu VA, Sanyal PK, Tewary S, Nilesh K, Suresh Prasad RM, Pawashe K. A split-mouth clinico-radiographic comparative study for evaluation of crestal bone and peri-implant soft tissues in immediately loaded implants with and without platelet-rich plasma bioactivation. *J Dent Res Dent Clin Dent Prospects*. 2019;13(2):117-122.
56. Temmerman A, Cleeren GJ, Castro AB, Teughels W, Quirynen M. L-PRF for increasing the width of keratinized mucosa around implants: a split-mouth, randomized, controlled pilot clinical trial. *J Periodontal Res*. 2018;53(5):793-800.
57. Cheruvu RNS, Katuri KK, Dhulipalla R, Kolaparthy L, Adurty C, Thota KM. Evaluation of soft tissue and crestal bone changes around non-submerged implants with and without a platelet-rich fibrin membrane: a randomized controlled clinical trial. *Dent Med Probl*. 2023;60(3):437-443.
58. Lyris V, Millen C, Besi E, Pace-Balzan A. Effect of leukocyte and platelet rich fibrin (L-PRF) on stability of dental implants. A systematic review and meta-analysis. *Br J Oral Maxillofac Surg*. 2021;59(10):1130-1139.

How to cite this article: Ivanovski S, Lee RSB, Fernandez-Medina T, Pinto N, Andrade C, Quirynen M. Impact of autologous platelet concentrates on the osseointegration of dental implants. *Periodontology 2000*. 2024;00:1-16. doi:10.1111/prd.12563