(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 4, Issue 5, Page No: 1489-1501
September-October 2021

IJMSCR

Platelet Rich Fibrin (PRF) Enriched Implants: A Futuristic Approach To Implant Dentistry

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Background: Dental implants play a major role in modern dentistry. It is considered to be a more sustainable replacement for lost natural teeth. Thus, the survival and success of the implants is very crucial, which depends on the phenomenon called 'Osseointegration'. Biofunctionalization of the implant surface has major role in osseointegration, which can be done by using various materials and platelet concentrates are one of them. This review aims to understand the process of osseointegration and the effect of platelet rich fibrin (PRF) enriched implants on it.

Conclusions: Biofunctionalization of the implant surface by using PRF, can be a definitive measure used in implant dentistry for better survival and success of the implant. Although it solely does not contribute to the success of the implant. The combined effect of host factors and properties of implant, is responsible for the superior outcome of implants.

Keywords: Biofunctionalization, Growth factors, Immediate placement, Osseointegration, Platelet rich fibrin, Review (narrative)

INTRODUCTION

The most common dilemma of any treating clinician is the decision whether to preserve the natural tooth or to extract the tooth and replace it with a single dental implant.[1] Dental implants provide a very predictable, effective, and reliable alternative for lost tooth.[2] Dental implants are considered to be the reliable alternative for the lost teeth as they mimic the natural tooth both functionally and aesthetically.

The first evidence of dental implants is attributed to the Mayan population roughly around 600 AD where they utilized pieces of shells as implants as a replacement for mandibular teeth.[3] In 1978, Dr. P. Branemark presented a two-stage threaded titanium root-form implant and tested a system using pure titanium screws which he termed fixtures.[4] He also proposed a concept of 'Osseointegration' and defined it as "a direct connection between living bone and a load-carrying endosseous implant at the light microscopic level."[5] A cascade of cellular and extracellular biological events occur at the bone-implant interface leading to osseointegration of implants, which are influenced by a number of factors.[6] These factors are divided into 3 major categories[7] as shown in figure 1.

At the microscopic level, the biomechanical interlocking between implant and bone can be influenced by the topography of an implant surface and thus a huge amount of research has been done on the surface topography of implants.[8] It includes macroscopic, microscopic and nanometric

characteristics of the implant surface.[9] Schwartz et al[10] found that osteoblast proliferation was increased on rough surfaces, which was supported by Albrektsson and Wennerberg,[8] who also demonstrated that fibroblast adhesion was weaker on rough surfaces. The current trend is to modify implant surfaces in order to improve cell-implant surface interaction, which leads to an increase in local bone density and acceleration of healing time.[11] A very recent attempt to modify implant surface was to coat surfaces with bioactive molecules such as bone morphogenetic proteins (BMPs), to further speed the quality of new bone formation.[12]

Platelet concentrates have been known for their incredible role in regeneration of soft as well as hard tissues supporting tooth. Thus, platelet concentrates like platelet rich fibrin (PRF) and its derivatives were more focused since last decade, to provide a favorable environment for osseointegration of dental implants, leading to a great success and survival of dental implants. Interestingly, it has been demonstrated that platelet concentrates have specifically a more pronounced effect on soft tissue wound healing when compared to hard tissues due to their incorporation of various growth factors including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β).[13] Recent evidence shows that the use of platelet concentrates like PRF and similar substrates can be employed in conjunction to immediate implants for preservation of marginal bone structure and peri-implant soft tissue condition.[14] Thus, this review aims to understand the process of osseointegration and the effect of platelet rich fibrin (PRF) enriched implants on it.

OSSEOINTEGRATION- CRUCIAL TO DENTAL IMPLANTS:

The concept of osseointegration, also been called "functional ankylosis", was modified by various authors and in 2012, Zarb and Koka defined osseointegration as "a time-dependent healing process whereby clinically asymptomatic rigid fixation of alloplastic materials is achieved and maintained in bone during functional loading."[15] Implant acts as a foreign body, to which the surrounding tissues respond and biological stability (osseointegration) is obtained, resulting in the formation of new bone tissue on the implant surface.[16] Osteogenesis between native bone and implant surface occurs in two direction, one is referred as 'contact osteogenesis' which means formation of bone from implant surface and the other one is referred as 'distant osteogenesis' which means formation of bone from bone surface.[16]

Immediately after placement of implant (within 2 hours), the space between implant and bone surface is filled with blood coagulum which contains a large number of erythrocytes as well as few macrophages and neutrophils within a fibrin network. By the end of 4th day, the coagulum is completely replaced by a newly formed tissue, containing a vascular structure with surrounding mesenchymal cells and few inflammatory cells. After a week, provisional matrix is formed which contains areas of newly formed woven bone. This matrix is rich in collagen fibrils and sprouting vascular structures surrounded by scattered inflammatory cells. The woven bone is lined by osteoblasts and contains osteocytes within it. By the end of 4th week, this newly formed mineralized tissue is extended from the cut bone surface and projected towards the implant surface. The central portion is filled with a primary spongiosa, rich in vascular structures and various morphotypes of fibroblast-like cells. The newly formed bone contains woven bone often combined with both parallel-fibered and lamellar bone.[17] These events are illustrated in figure 2.

BIOFUNCTIONALIZATION- MODIFYING THE IMPLANT SURFACE:

Osseointegration of the implant is mediated by biochemical interactions between cells and the implant surface, by coating with components of extracellular bone matrix (ECM) to enhance implant integration and bone healing. Cytokines, growth factors, and integrins are able to interact with bone cells and influence migration, growth, adhesion, and differentiation.[18] It is suggested that the biofunctionalization of implant surface may interfere in the acceptance and bonding of the implant to the surrounding bone. It involves biochemical modifications of implant surface, such as the immobilization of proteins, enzymes, or peptides.[19]

There are three methods, by which biochemical modification of an implant surface is performed to

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control concentration, retention, and/or release of molecules from implant surfaces, namely, physisorption, covalent binding, and carrier system.[20] Physisorption is a phenomenon of spontaneous adsorption on the surface caused by electrostatic and van der Waals forces,[21] while few molecules can be incorporated onto the implant surface either by covalent binding[22] or by direct integration into the coating material, which acts as a carrier system.[23] Literature shows the use of different materials for biofunctionalization of implant surface for better osseointegration and wound healing, which are hydroxyapatite,[24] calcium phosphate,[25] polyethylene glycol,[26] type I collagen,[27] bone morphogenic proteins,[28] peptides like RGD (Arginine-glycine-asparginic acid sequence) peptide[29]. Currently, various platelet concentrates have been used for the biofunctionalization of implant surface. The use of these platelet concentrates, have made the success of implants, to be more predictable than before. Also, it has given a hope to clinicians, to reduce the failure of implants due to improper osseointegration.

PLATELET CONCENTRATES- A BOON TO IMPLANT DENTISTRY:

Platelet concentrates collected from whole blood was first introduced over 20 years ago and the concept was developed to utilize human blood proteins as a source of growth factors, capable of supporting angiogenesis and tissue ingrowth.[30] The journey of platelet concentrates started from 1954, when Kingsley [31] used the term Platelet Rich Plasma (PRP) which is the first generation of platelet concentrates to earmark thrombocyte concentrate during experiments related to blood coagulation. In 1986 Knighton et al [32] first demonstrated that platelet concentrate successfully promote healing and they termed it as "platelet-derived wound healing factors (PDWHF)", which was later changed to the term "platelet-derived wound healing formula (PDWHF)."[33] In 2000, Choukroun et al[34] developed another form of platelet concentrate in France which was labeled as Platelet Rich Fibrin (PRF), which is termed as second generation of platelet concentrates. Recently, advanced PRF (A-PRF) by Choukroun et al[35] and Titanium prepared PRF (T-PRF) by Tunali et al[36] was introduced in 2014.

PRF consists of three main components, 1. Cells like platelets, leukocytes, macrophages, granulocytes, and neutrophils; 2. Three-dimensional provisional extracellular matrix, 3. Bioactive molecules (growth factors) like transforming growth factor beta (TGF-β), platelet derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), insulin growth factor (IGF), and epidermal growth factor (EGF).[37] Leukocytes play a very important role in wound healing due to their key importance during anti-infectious pathogen resistance as well as their implications in immune regulation.[38] Growth factors can either stimulate or inhibit cellular migration, adhesion, proliferation, and differentiation and blood serves as the main reservoir of numerous growth factors and cytokines, promoting angiogenesis and tissue regeneration for wound healing.[39]

PRF is considered as a healing biomaterial which is commonly used in implant and plastic periodontal surgery procedures to enhance bone regeneration and soft-tissue wound healing.[40-41] There are two possible mechanisms by which PRF enhances wound healing given by Chang et al,[42] depicted in figure 3.

In a study done by W. K. Hafez et al (2014),[43] PRF was successfully used as a membrane as well as mixed with bone graft, for coverage of immediate implants in the maxillary anterior region. Recently, various studies have been done to evaluate the efficacy of PRF coated implants on wound healing and osseointegration. Table 1, represents the methodology and outcomes of these studies. All of these studies concluded that different forms of PRF can be used during implant insertion for better implant stability, soft tissue and hard tissue healing, bone to implant contact, cell migration, except a study done by Kriti Banerjee et al (2019),[44] which proposed that there is no difference between PRF coated and noncoated implants.

CONCLUSION:

PRF, a healing biomaterial can be used in many ways in implant dentistry. When it is used during implant insertion in the form of a gel or coating over implant surface, it enhances the wound healing as well as osseointegration of the implant. PRF technology has grabbed the attention of clinicians because it is derived from the patients' own blood, while being

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financially realistic for the patient and the clinician, and with virtually no risk of a rejection reaction (foreign body response). Thus, it can be a definitive measure used in implant dentistry for better survival and success of the implant. Although very few clinical trials have been done to prove the effect of PRF enriched implants, it is an area of interest for many researchers. However, biofunctionalization of implants solely does not contribute to the success of the implant. The combined effect of host factors and properties of implant, is responsible for the superior outcome of implants.

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Table 1. Various studies on PRF coated implants

Author And Year	Aim Of the Study	Platelet Concentrate Used to Coat Implant	Methodology	Conclusion

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Elif Oncu et al (2015)[45]	To evaluate the effects of PRF application on implant osseointegration in early healing	Acellular plasma portion of PRF	20 healthy patients. Two or more adjacent missing teeth, extracted at least 6 months previously. Test group (PRF+): placement of PRF membrane in one of the sockets followed by placement of implant coated with acellular plasma portion of PRF Control group (PRF-): placement of implant without any PRF	Mean implant stability quotients (ISQs) of PRF+ implants after 1 week and 4 weeks > Mean ISQs of PRF- implants after 1 week and 4 weeks
Elif Oncu et al (2016)[46]	To evaluate the leucocyte- and platelet-rich fibrin (L-PRF) induced osseointegration and bone-implant contact (BIC) in an experimental animal model	L-PRF	Twelve 4-month-old New Zealand white rabbits with two implant cavities in each tibia (total 4 implant cavities prepared per animal) Test group: L-PRF membrane placed into implant cavities and remaining L-PRF used t soak implants and then placed int L-PRF coated implant	Application of L-PRF increased the rate and amount of new bone formation in the test group compared to the control group. Bone-to-implant contact was enhanced when the implant surface was pre-wetted with L-PRF

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			cavities Control group: placement of implants without any use of L-PRF	
Xuzhu Wang et al (2017)[47]	To compare injectable-platelet-rich fibrin (i-PRF) with platelet-rich plasma (PRP) on the behavior of gingival fibroblasts cultured on smooth and roughened titanium implant surfaces	i-PRF	This study compared i-PRF to the clinically utilized PRP and characterized the behavior of human gingival fibroblast cell viability, migration, proliferation and messenger RNA (mRNA) levels of growth factors (PDGF, TGF-β1, fibronectin and collagen1), as well as collagen1 matrix synthesis	i-PRF induced significantly higher cell migration, as well as higher messenger RNA (mRNA) levels of PDGF, TGF-β, collagen1 and fibronectin when compared to PRP. Collagen1 synthesis was highest in the i-PRF
Manoti Sehgal et al (2018)[14]	To present the clinical application of immediate implant placement with L-PRF and immediate	PRF gel	The retained deciduous teeth were extracted. Implant coated with PRF gel was placed immediately followed by placement of the L-PRF membrane using the poncho technique.	The use of PRF for the maintenance of crestal bone and soft tissue at the implant sites provided an adequate clinical condition for better esthetics

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	prosthetic loading in anterior esthetic region			associated with immediate implant placement
Marco Lollobrigi-da et al (2018)[48]	To assess the behavior of different implant surfaces when in contact with two liquid leucocyte- and platelet-rich fibrin (L-PRF) products	Liquid L-PRF	Six commercial pure titanium discs Three discs: micro/nano rough surface; three discs: machined surface Testing of three protocols involving the immersion of the samples in (1) platelets, lymphocytes, and fibrinogen liquid concentrate (PLyF) for 10 minutes, (2) an exudate obtained from L-PRF clots rich in fibronectin and vitronectin for 5 minutes, and (3) the fibronectin/vitronectin exudate for 2 minutes followed by immersion in the PLyF concentrate for	The contact of a micro/nano-rough implant surface with a liquid blood concentrate allows formation of a stable fibrin layer containing platelets and leucocytes. Fibrin clot formation may be further supported by adjunctive pretreatment of samples with an exudate containing fibronectin and vitronectin

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			further 8 minutes. Observed using a scanning electron microscope (SEM)	
Kriti Banerjee et al (2019)[44]	To compare and evaluate the clinical and radiographic parameters of PRF coated and non-coated implants	PRF gel	20 implants. Two-stage surgical protocol with or without PRF liquid and PRF gel application.	Coating the implant fixtures with PRF liquid does not enhance the bone regeneration when compared with conventionally placed implants without the use of PRF
Renu Gupta et al (2019) [49]	To evaluate the effects of PRF application on short implant both clinically and radiologically	PRF	A total of fifteen short implants. After osteotomy site preparation, it was rinsed with PRF serum and gelatinous PRF was placed inside it, followed by implant placement in osteotomy site.	The use of PRF along with short implants is an important adjunct in implantology as it accelerates the soft and hard tissue healing around the implant without performing any extensive surgery in deficient bone height.
Lorenzo	To evaluate	PRF	Grade IV titanium	PRF and

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Bevilacqua et al (2021)[50]	blood wettability on The different kinds of surfaces, brand new and after treatments		disks Five machined, laser-treated and sandblasted each Four steps included-1: no treatment; 2: surface instrumentation with an ultrasonic titanium tip; 3: platelet-rich fibrin (PRF) coating and drying with sterile gauze; 4: etching with phosphoric acid, rinse and saline solution and air-drying. At the end of each step, a 4 µL blood drop placed on the surfaces Contact angle was calculated	phosphoric acid used for conditioning exposed implant surfaces can be used for the healing of peri-implant tissues.

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Figure 1. Factors affecting osseointegration

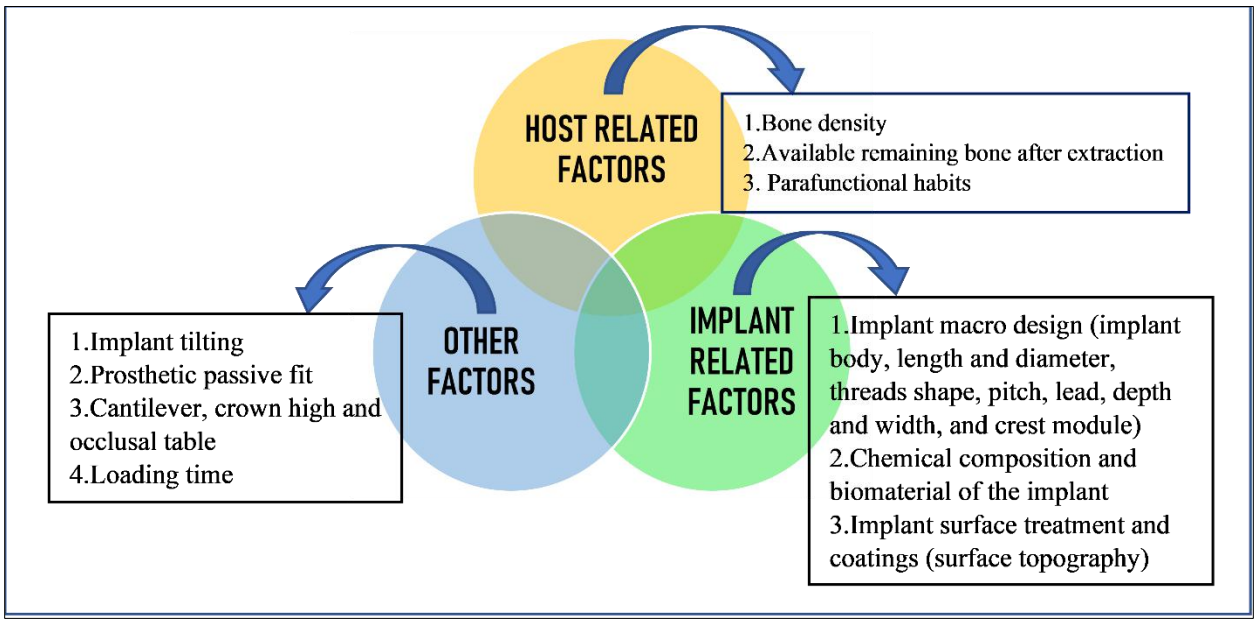

Figure 2. Step by step events occurring between bone-implant surface during osseointegration

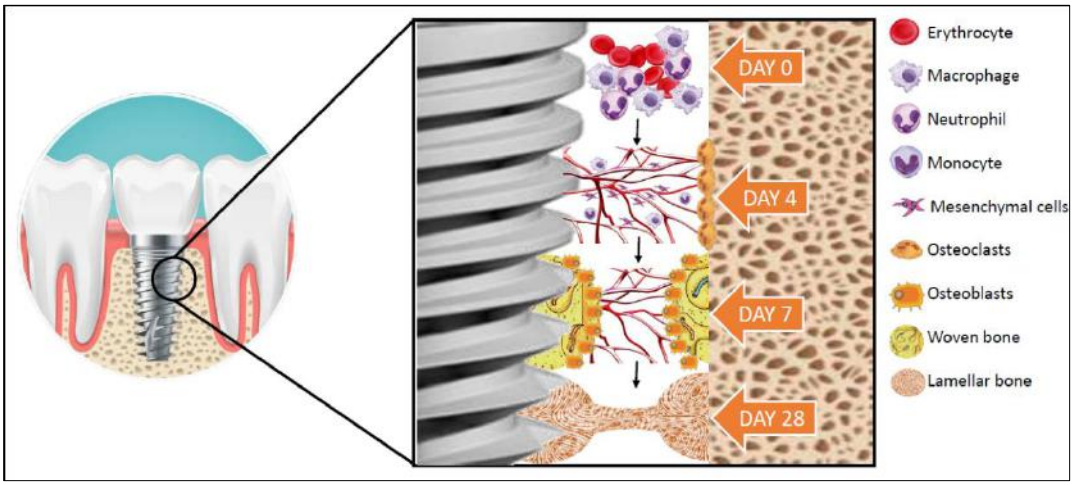

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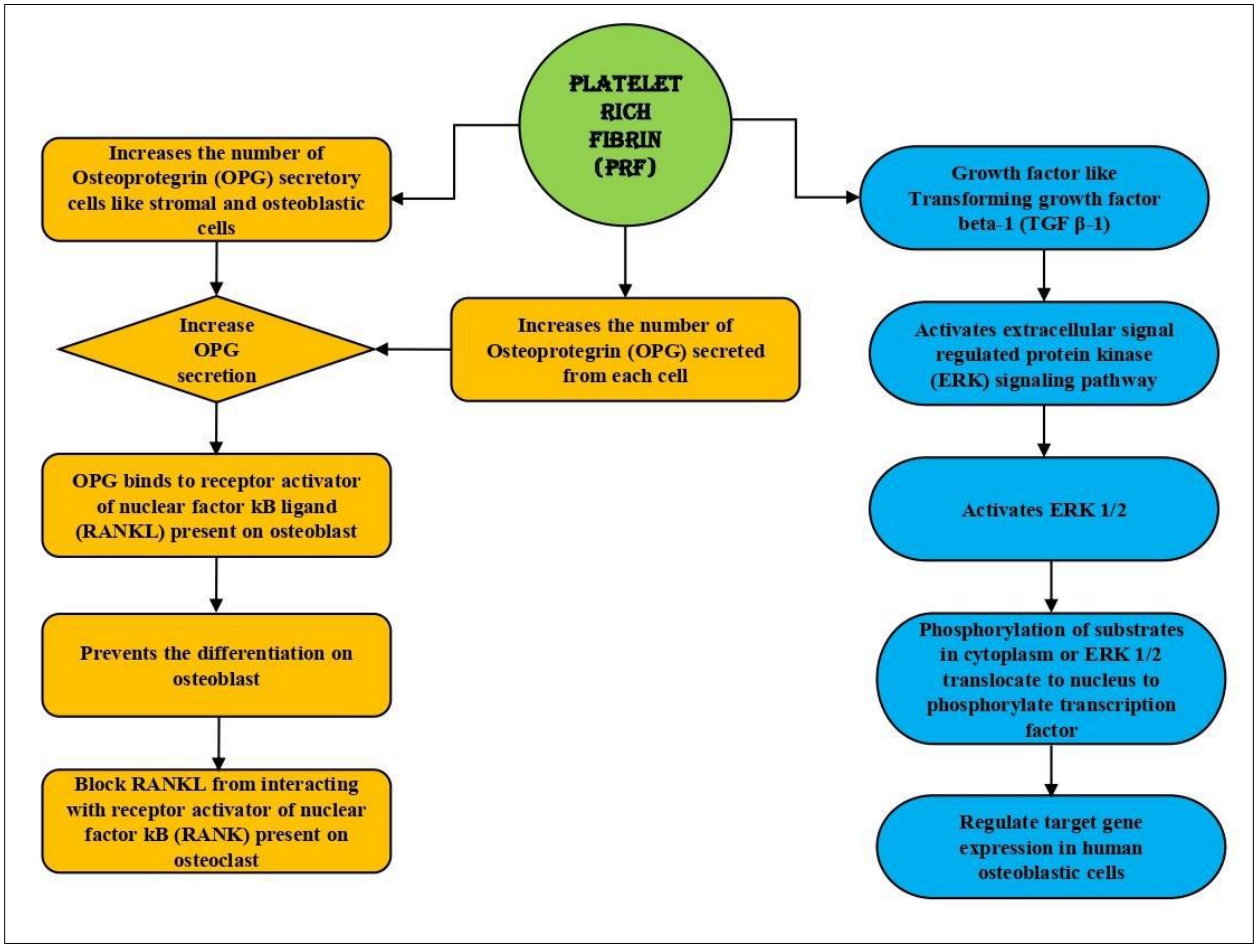
Figure 3. Mechanism of action of PRF



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