Review

A Comprehensive Review on Efficacy of Leukocyte and Platelet-rich Fibrin (L-PRF) Administration in Reconstruction of Oral and Maxillofacial Structures

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ABSTRACT

Several studies have shown that growth factors are effective in soothing inflammatory processes involved in the initial hemostasis phase of wound healing. Leukocyte and platelet-rich fibrin (L-PRF) is the second generation of concentrated platelets that have been shown to stimulate the proliferation of osteoblasts, gingival fibroblasts, and periodontal ligament cells. Rich platelet components have an immune function and antibacterial properties, which play a critical role in the wound healing process. The present study aimed to review the reported documents on L-PRF administration in regeneration and wound healing of oral and maxillofacial surgeries. The research was performed using well-known medical databases to find controlled clinical trials that used L-PRF as a co-treatment strategy during oral and maxillofacial surgeries. Eligible articles published between 2000 and 2022 in PubMed, Web of Science, Science Direct, and Scopus databases were selected for this review. According to the results of this study, L-PRF has significant effectiveness as a maxillofacial regenerative therapy by improving para-clinical parameters after surgery. However, more clinical practice and additional research are essential for the development of this complementary treatment method.

Keywords L-PRF, Maxillofacial, Oral, Reconstruction, Wound healing

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Introduction

The maxillofacial structures are always at risk of damage by various types of traumas, including injuries caused by vehicle accidents, quarrels, falls from height, and sports injuries [1]. Fracture healing involves a series of complex processes of cell and tissue proliferation, displacement, and differentiation [2]. Growth factors, inflammatory cytokines, antioxidants, osteoblast and osteoclast cells, hormones, amino acids, and numerous nutrients are known to be the main accelerating agents of complex processes in fracture repair [3]. Several growth factors are involved in the physiological process of wound healing after fractures and surgery, including platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF1 and IGF2), vascular endothelial growth factor (VEGF), and keratinocyte growth factor (KGF) [4-5].

Autologous platelet concentrates (APCs) were used in oral surgery in 1991 to improve bone regeneration [6]. In general, autologous platelet is divided into four categories: platelet-rich plasma (PRP), platelet-rich fibrin (PRF), plasma rich in growth factors (PRGF), and concentrated growth factors (GCF) [7].

Despite the growing success of PRP administration, several limitations have been reported, such as the procedure being time-consuming. Accordingly, to prevent the coagulation process, anticoagulants, such as CaCl2, are used, which is a potent inhibitor of wound healing [8]. Moreover, some studies have reported uncontrollable release of growth factors after PRP administration [9-10]. These limitations have led researchers to find other methods to improve tissue regeneration.

The PRF is the second generation of the APC family, first introduced in 2000 by Choukroun et al. [11]. The PRF was later renamed Leukocyte and platelet-rich fibrin (L-PRF) or PRF-Leukocyte due to its high leukocyte content. The L-PRF processing technique lacks anticoagulants and has a shorter preparation time [12]. Since no anticoagulant is used in this method, a three-dimensional fibrin bio-scaffold called L-PRF is created [13]. Moreover, L-PRF is a solid biomaterial which does not dissolve rapidly in solution after consumption. These properties help maintain the scaffold of the platelet and leukocyte growth factors and thus increase the lifespan of cytokines [14].

For a long time, several studies have been conducted with the aim of advancing and developing treatment methods to accelerate recovery, reduce complications, and improve function in patients after surgery. In this regard, several applications of L-PRF have been reported in previous studies. Accordingly, this review aimed to present a comprehensive survey on L-PRF efficacy in oral and maxillofacial surgeries.

Materials and Methods

This research was conducted by two investigators through scientific articles indexed in databases, including PubMed, Web of Science, Science Direct, and Scopus, which were published between 2000 and 2022. The search keywords were combinations of L-PRF, surgery, wound healing, reconstruction, regeneration, maxillofacial, and oral. The interventional studies on the human population were included. However, the publications evaluating the effect of L-PRF on other organ disorders, animal studies, dissertations, books, abstracts of conferences, and patents were excluded.

Medication-Related Osteonecrosis of the Jaw (MRONJ)

The main target of treating patients with Medication-Related Osteonecrosis of the Jaw **(**MRONJ) is to maintain their quality of life, especially in patients with another active disease [15-16]. In these patients, pain control, infection management, and enhancement of surrounding bone healing are the main concerns. Conservative treatment, however, may resolve the patient's complaints. However, in some cases, the damaged bone showed no improvements, and alternative and adjuvant therapy may be necessary [17]. The American Society of Maxillofacial Surgeons (AAOM) presented a classification for MRONJ in 2014 [18]. According to this classification, MRONJ is divided into five stages. Symptoms of the first stage, or the "at-risk" stage, include the absence of exposed bone in the patient's mouth without symptoms that have been injected with bisphosphonate injection [19]. In the last stage, all the symptoms of the disease, such as ossification, accompanied by the patient's other symptoms, such as pain, infection, internal fistulas, extra-oral, and even fractures are observed [20]. The AAOM report also states that the risk of developing this disease in patients consuming bisphosphonates is 0.00038 to 0.1 percent [21]. In patients who have used bisphosphonates for more than four years, this risk increases to 0.21 percent [22]. The MRONJ treatment varies according to the progression of the disease. Recommended treatments for MRONJ include a range of conservative treatments such as using mouthwash, practicing hygiene, and administrating antibiotics to more invasive treatments (e.g., hysterectomy and hyperbaric oxygen). Laser therapy, Ozone therapy, and APCs are among the novel treatments [23].

Various studies have examined the effect of APCs on maxillofacial treatments. The APCs can have beneficial effects on soft tissue healing after various surgeries, such as cosmetic surgeries, periodontal treatments, pre-implants, and sinus lifts [24-25]. Due to the excellent effect of APCs on soft and hard tissue improvement, the use of these materials in various studies has been suggested for MRONJ treatment [26]. Unfortunately, a study to compare the therapeutic effect of PRF and other methods such as Ozone therapy, laser therapy, and the use of hyperbaric oxygen MRONJ has not been conducted yet [27]. However, it should be mentioned in studies on the effect of Ozone on MRONJ that due to requiring more sessions for treatment, this method imposes a higher cost on patients [28]. The success rate of Ozone treatment has been controversial in studies [29]. In addition, the number of these studies is limited, and the result is definite. Although, the latest studies, using laser treatment along with the usual facial surgery show no significant beneficial effect [30]. Considering the failure of the lesion to respond to Ozone treatment as well as the higher cost and the longer duration of treatments, the surgical team concluded that the best treatment for this patient was PRF administration.

Fernando et al. reported results on the treatment of 11 MRONJ patients. In this study, PRF was placed on a bone defect for all the patients, and their treatment outcome was completely successful [31]. One- to three-year follow-ups showed no signs of recurrence of the disease. Dincă et al. also reported that 10 MRONJ patients were successfully treated [32]. Moreover, Uckan and Soydan reported successful treatment of MRONJ with PRF [33]. Although the authors stated that the results of their studies may not be significant, bu the data are consistent with pervious litratures. Factors such as the stage of the disease, the patient's age, and the location of the lesion can affect the treatment success.

A clinical trial by Asaka et al. was performed on 102 patients [34]. In this Japanese study, patients were divided into two groups, one group received surgical treatment and PRF, and the other group only received surgical treatment. Their findings showed that PRF significantly affected wound healing and tooth repair. Giudice et al., in a similar study on 47 patients in Italy, reported the significant efficacy of PRF on MRONJ treatment [35]. Hartlev et al. documented a high success rate in the treatment of 15 patients with MRONJ and PRF treatment after surgery [36]. Kim et al. also reported the beneficial effect of PRF on 34 patients with MRONJ after debridement surgery [37].

Tooth Extraction

Tooth extraction is one of the main oral surgery procedures associated with some physiological changes through the alveolar process. These processes can affect the alveolar bone structure [38]. Several postoperative risk factores could affect the soft and hard tissues, including infection, pain, bleeding, and late recovery. The absorption process starts six months after the tooth extraction and might continues by the rest life of the patient. Bone regeneration methods include bone morphogenetic proteins (BMPs), mesenchymal stem cells, biomaterials, and some active molecules [39-40].

Previous studies showed the positive and beneficial effects of PRF administration in bone regeneration to promot dental sockets [38, 39, 41, 42, 43] and accelerate soft tissue healing [38, 41, 44, 45], although some studies [46] demonstrated no beneficial properties in bone healing subsequent to tooth extraction. First of all, the impact of L-PRF on bone regeneration was evaluated quantitatively via assessing three review articles [38, 46]. A study by Al-Hamed et al. [47] reported that administration of PRF showed no significant effect on bone regeneration.

Conversely, both studies by Del Fabbro et al. [38] in 2014 and 2017 [39], documented that PRF administration showed remarkable posetive effect on bone regeneration. Moreover, the activity of osteoblast was assessed by a meta-analysis review [42]. The PRF treatment did not show any significant influence on osteoblast activity. However, other systematic reviews [43, 47, 48] reported significant performance of the PRF treatment in diminishing vertical and horizontal changes. In this context, some systematic reviews [38, 42, and 45] documented a remarkable enhancement effect of PRF on epithelization and soft tissue healing at the first week of extraction.

A systematic review assessed the pain parameter using meta-analysis. The PRF treatment significantly decreased pain in patients after tooth extraction [43]. A study by Al-Hamed et al. [49] reported significant relief of pain after tooth extraction. Another study [23] observed a lower amount of analgesic drug consumption in patients with sockets preserved with PRF administration. A study by Canellas et al. [14] documented the effect of PRF on alveolar osteitis. The results showed that PRF treatment significantly diminished the occurrence of osteitis after the extractions. Another study by He et al. [43] documented the effect of PRF on trismus. The use of PRF had no effect on the patients with trismus. In contrast, Castro et al. [42] showed a significant positive property of PRF on trismus.

Dental Implants

There are some clinical factors that affect the aesthetic success of implant-supported prostheses, especially the main risk area being the anterior maxilla. Implant positioning, the manipulation of the soft tissue, and the type of prosthesis are the main factors that depend on the dental surgeon’s performance. The other factors depend on the quantity and quality of bone and soft tissues in each person [50].

The soft tissue structure depends on the structure of the bone, which will lead to the shape and anatomy of the region. Any defect of the bone structure can cause aesthetic failure due to the gingival structure accompanying the bone condition [51]. This structure deficit shown in dental extractions or the appearance of longitudinal fractures and fistulas, mainly compromising the vestibular bone structure, leads to a loss of well-defined structure [52].

The clinical assessments of the bone structure condition after extraction documented a loss of alveolar volume after the procedure. Accordingly, the aesthetic search of implants installed in the anterior maxilla area cannot be easily achieved. Over 50% of the border width shows a reduction during the first six months after extraction. In the case of vestibular wall involvement, the incidence percentage can be higher [53].

Multiple studies attempted to prevent and control bone loss after tooths extraction. Crest preservation could reduce the reabsorption of the buccal wall and enhance bone formation within the alveolus. However, there is no evidence to document significant preservation of the structure. In this regard, previous studies report that some structural preservation methods were successful in decreasing the vertical and horizontal loss of the alveolar bone crest after extraction [54]. The main point of structure-preserving is directly related to the search for aesthetic results and healthy structures around the implant. The buccal wall reabsorption may lead to aesthetic failure, causing the weak appearance of soft tissues [55]. A significant response impact was found in the buccal bone thickness of the anterior region of the maxilla and the adjacent soft tissues after extraction.

In this context, PRF showed some advantages in dental implants, including the acceleration of the cicatricial process after dental implants and tissue regeneration. Several studies reported that PRF treatment has properties in transforming adult stem cells into specific cells for the formation of bone and gingival tissues; the ability to regenerate the tissue vascularization network and the need to remove bone from another part of the body for bone grafting may be possible, making the procedure more comfortable for the patient [56-57].

Maxillofacial Bone Graft

The maxillofacial bone is a critical region for traumas, tumor predilections, inflammatory processes, and congenital disorders. Any defect of oral and maxillofacial structures that occurs by diseases, including atrophy in alveolar bone subsequent to tooth loss, removal of bone during tumor surgeries, periapical bone destruction caused by periapical periodontitis, and alveolar cleft, have mainly affected the mental and physical state of the patients. Several studies were carried out on oral and maxillofacial bone reconstruction using various bone graft materials, such as synthetic materials or natural materials (e.g., autologous bone and allogeneic bone). Autogenous bone transplantation, which is defined as the gold standard treatment strategy, was limited to the regeneration of maxillofacial bone due to restricted donor supply and chronic pain complaints in patients [58].

According to recent studies, L-PRF has shown considerable efficiency in oral and maxillofacial bone regeneration [59]. The L-PRF contains macrophages that could directly affect osteogenesis promotion by modifying nuclear factor kappa B gene expression [60]. Macrophages have the potential to support the activity of bone formation and construction by maintaining the local availability of mesenchymal stromal/progenitor cells while recognizing and removing apoptotic osteoblasts to trigger a paracrine loop [61]. Moreover, it has been documented that platelets and leukocytes accelerate bone reconstruction by stimulating the production and activation of cytokines [62]. The TGF-β1 is one of the main growth factors in L-PRF, which may promote the formation of new bone by stimulating the biosynthesis of collagen and fibronectin [63]. Collagen is an important component of the bone, and fibronectin is a stimulator for increasing cell adhesion and migration process to promote osteogenic differentiation through controlling the Wnt/β-catenin signaling transduction [64-65]. Another factor is vascular endothelial growth factor (VEGF), which affects the angiogenesis process, so it seems necessary for skeletal development [66]. Other essential biomolecules components of L-PRF are BMP-1, PDGFs, and IGF-I, which are involved in extracellular matrix deposition, increasing the proliferation and differentiation of osteoblasts, respectively [67].

Moreover, the 3-dimensional structure of L-PRF can prepare a conducive bio-scaffold to osteogenesis. The L-PRF also has a special connective construction of fibers which provides a flexible and thin network of fibrin for cell migration and capture of cytokines [68]. Since the matrix of fibrin within L-PRF start to remodel, it can lead to gradual releases of cytokines [69]. These properties can cause increases in cell proliferation during bone formation [70].

In recent years, some L-PRF graft components improved in structure, and some application limitations were removed as well. However, future experimental design studies are essential to improve the preparation process of L-PRF and clarify the mechanism of L-PRF action in bone regeneration. In this context, multiple studies on the augmentation of the maxillary sinus reported significant results based on L-administration. However, control group deficiency was often considered to undermine the conclusions. The L-PRF was used for maxillary sinus augmentation in two clinical studies [71-72], which showed that PRF has beneficial properties in bone regeneration. On the other hand, a case report study reported that after treatment with PRF, the results obtained from a 59-year-old patient showed that the sinus cavity around the implants was full of dense bone-like tissue. Surprisingly, in this patient, the osteocytes were reported to be dispersed in the newly formed bone tissue [71].

Moreover, in another study [72] on 27 patients, in which two kinds of implants were applied, it was shown that residual bone in the sandblasted acid-etched (SA) and hydroxyapatite (HA) groups were enhanced. Furthermore, the L-PRF administration caused reduced bone formation during sinus elevation caused by perforation of the sinus membrane [73]. Although there was no significant perforation in the mentioned study, the PRF was considered to have a protective effect on the sinus membrane, which can cause sinus augmentation. Additionally, two clinical trials on PRF administration in intra-bony defects after cystic enucleation showed remarkable radiographic osseous regeneration during the first, third, and sixth months of follow-ups on all patients [74-75]. Moreover, some case report studies that used L-PRF to treat intra-bony defects [76-77] demonstrated significant bone fill compared to the routine treatment. However, a study by Nagaveni et al. [78] reported that radiograph results showed no significant differences in bone fill in the L-PRF treated group compared to the adjacent normal teeth.

The results of some case reports [79-81] on 28 patients who were treated with L-PRF combined with other bone graft materials have shown significant bone regeneration using histomorphometric or imaging examination in all patients. The disorders included in this study were bony defects induced by periapical inflammatory lesions, augmentation of the maxillary sinus, molar teeth extraction, and intra-bony defects. On the other hand, a study by Pichotano et al. [82] on a patient for maxillary sinus augmentation in which the right sinus was filled with L-PRF and deproteinized bovine bone mineral (DBBM], and CM, while the left side was filled with DBBM and CM, the obtained results showed a significantly higher proportion of bone formation in response to L-PRF administration using histo-morphometric analysis.

In this context, some controlled trials [83-84] reported more osteogenesis properties when L-PRF was combined with bone graft materials in comparison with materials treated or L-PRF treated alone. However, in other studies, the aim of combined materials with L-PRF [85] was to achiving to osteoconductive properties, improve effective space maintenance, and prepare factors and cells. In some other studies, the efficacy of L-PRF on graft materials was reported [82, 84] by increasing circulating stem cells, cytokines, platelets, and leukocytes. The results of the mentioned studies suggested that L-PRF may play the role of a delivery system for graft particles within the maxillary sinus floor augmentation.

The consuming time for the formation of new bone is related to the volume of the graft. Some biomolecules, such as fibrin, could help to exclude the dispersion of the Bio-Oss particles. Accordingly, the sinus graft material is lesser required to achieve the suitable vertical height of the material for implant placement.

In contrast, other controlled trial studies [86-88] demonstrated that L-PRF administration failed to increase bone formation when combined with other graft materials. In this regard, a study by Sezgin et al. [86] showed that ABBM might have prevented the effect on the positive properties of L-PRF. Moreover, Turkal et al. [87] reported no significant effect of EMD combined with PRF to provide effective space maintenance.

These results defined the reason for stopping the administration of L-PRF with other graft materials for additional bone gain. According to the above studies, it can be concluded that L-PRF has the ability to enhance osteogenesis.

Discussion

Concentrated platelet components are blood-clotting substances used to prevent and treat inflammatory processes after surgeries. The development of these procedures as bio-active surgical additives, which were used to improve wound healing, originated from fibrin adhesive molecules [89]. Since 1990, various platelet components which play a vital role in the wound healing process have been discovered in medical science [90]. In case of applying these products to the injured tissue or surgical area, it may lead to accelerating the wound healing process.

Wound healing occurs within two steps, including primary and secondary wound healings. In cuts wounds where the edges of the wound are stitched next to each other by suture thread, healing proceeds in a primary way. However, in wounds caused by severe injuries, in which vast damages are seen in the soft tissue or bones, healing occurs in a secondary way. Incisional wounds are created under controlled conditions with minimal bacterial contamination and tissue damage. This type of cuts causes focal and limited disintegration of the basement membrane, and a small number of cells and connective tissues are destroyed. As a result, the regeneration of the covering layer has a greater contribution to the healing process compared to the formation of fibrotic tissues [91]. In wounds with extensive tissue damage, the regeneration of epithelial cells alone cannot restore the lost structure. Therefore, the formation of granulation tissue and the accumulation of extracellular matrix and collagen are also added to the healing process [92]. Accordingly, using compounds and methods that can promote the speed of secondary wound healing, such as Platelet-rich plasma, have been considered.

Most reported studies on L-PRF have documented the beneficial effects of this treatment strategy on the improvement of post-operation oral and maxillofacial surgery processes. The platelet-rich components have been used to improve wound healing of soft tissues and bone. The advantages of L-PRF compared to PRP are low cost, simple preparation procedure, and easy application [93, 94].

Platelet aggregation and enhanced release factors play a key role in various stages of wound healing [95]. Therefore, platelet growth factors are used for improving wound healing in various surgeries, such as oral and orthopedics. Platelet components have a significant efficacy due to their direct effects on the stimulation of bone regeneration. Bone is a connective tissue that contains various cells within a bio-scaffold. Bone cells include osteoclasts, osteoblasts, osteocytes, osteogenic cells, and hematopoietic cells [96]. In cases of fractures, the process of bone repair and osteoporosis of osteoblasts are initiated with the secretion of various growth factors that are also found within platelets. In the early stages of fracture, platelets accumulate in the injury region, with an increase in the various growth factors, EGF, TGF-B, and PDGF play a critical role in bone regeneration [97].

The L-PRF is one of the platelet components which is widely used as an autogenous grafting material due to its potential for enhancing physiologic wound healing and new bone regeneration. Putting a fresh extraction socket with L-PRF prepares an efficient alternative treatment for implant site preparation. The results of studies show decreases in alveolar ridge resorption subsequent to tooth extraction. The L-PRF as the grafting material led to the augmentation of the maxillary sinus floor and the formation of new bone in the augmented site [98]. Clinical applications of the L-PRF membrane showed that as a solid material, it is easier to handle and position in a defective area compared to the PRP and other natural blood clots [99].

The strong fibrin component of the L-PRF membrane provides a good microenvironment to use it as a true membrane or tissue [100], whereas other platelet components are only applied as a transitory fibrin layer at the surgical site. Studies documented that the L-PRF membrane has the potential to release growth factors and matrix proteins after 7 days of administration [101]. Furthermore, the L-PRP, due to its rich leukocyte content, can improve the wound healing process and bone reconstruction through increases in proliferation, differentiation, immunity, and infection. The presence of leukocytes greatly impacts the biology of growth factor products, not only due to their immune system stimulation and antimicrobial potency but also because they are turntables of the wound healing process and regulation of local factors [102, 103]. It seems that due to the high fibrinogen content, platelet-enriched plasma reacts with thrombin and leads to the induction of fibrin clot formation. In this context, collagen synthesis in the increased Webster's extracellular matrix provides favorable conditions for cell migration and adhesion [104].

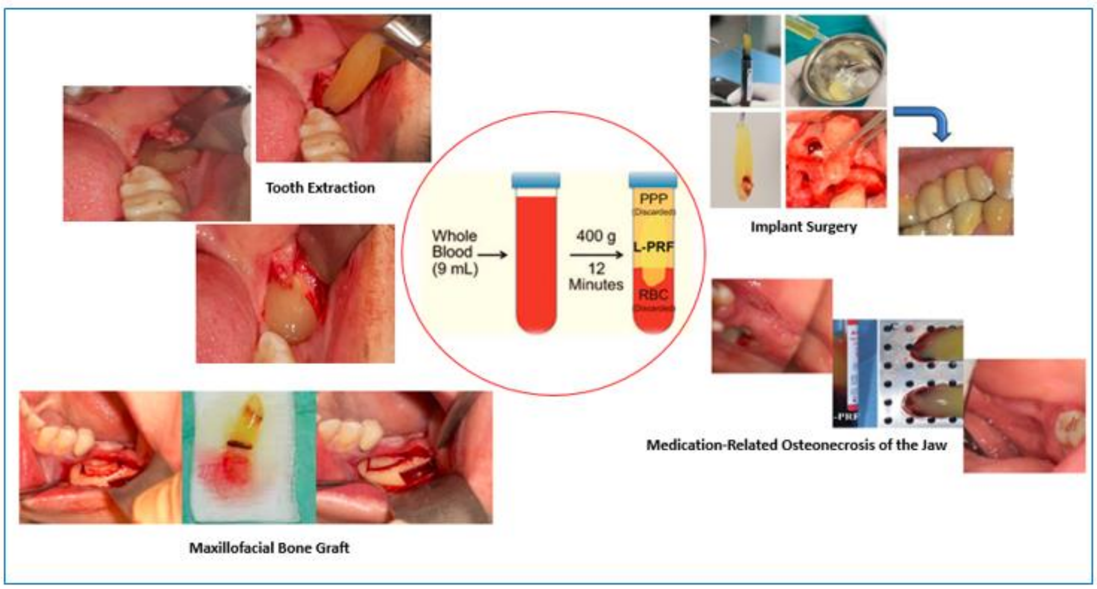

Figure 1. Application of platelet-rich fibrin (**PRF**] in oral and maxillofacial reconstruction

According to the related literature, L-PRF may affect the recovery process of patients via stimulating wound healing, accelerating recovery, and improving outcomes after surgeries. Since the infection around the wound region is one of the main reasons for delays in the healing process and tissue regeneration, L-PRF can be considered a potential strategy to fight infection and decrease healing times. Accordingly, it seems that L-PRF as a new approach will be widely developed to promote rapid wound healing in the near future. However, currently, L-PRF is used in many domains, including oral-maxillofacial surgery, periodontal surgery, plastic surgery, and orthopedic surgery, due to its low cost and easy applications. Clinical documents of L-PRF reported significant efficiency in extraction socket preservation [105], osseous regeneration after radicular cyst enucleation [106], sinus floor elevation, alveolar ridge preservation, and implant therapy [107], intra-bony defect repair, furcation defect repair, and periodontal plastic surgery [108].

In summary, according to the well-documented evidence (Figure 1), L-PRF is a key activator of many processes involved in tissue and bone regeneration, and more understanding of its properties is an essential issue for developing this biotechnology.

Conclusion

In summary, according to the well-documented evidence (Figure 1(, L-PRF is a key activator of many processes involved in tissue and bone regeneration, and more understanding of its properties is an essential issue for developing this biotechnology.

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Conflicts of interest

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