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

Alain Simonpieri[1], Marco Del Corso[1,2], Alain Vervelle[1], Ryo Jimbo[3,4], Francesco Inchingolo[5], Gilberto Sammartino[2] and David M. Dohan Ehrenfest[1,6,*]

[1]*The LoB5 Foundation for Research, Paris, France;* [2]*Department of Odontostomatological and Maxillofacial Sciences, University Federico II of Naples, Italy;* [3]*Department of Biomaterials, Institute for Clinical Sciences, The Sahlgrenska Academy at University of Gothenburg, Sweden;* [4]*Department of Prosthodontics, Faculty of Odontology, Malmö University, Malmö, Sweden;* [5]*Department of Dental Sciences and Surgery, University of Bari, Italy;* [6]*LoB5 unit, Chonnam National University School of Dentistry, Gwangju, South Korea*

Abstract: Platelet concentrates for surgical use are innovative tools of regenerative medicine, and were widely tested in oral and maxillofacial surgery. Unfortunately, the literature on the topic is contradictory and the published data are difficult to sort and interpret. In bone graft, implant and reconstructive surgery, the literature is particularly dense about the use of the various forms of Platelet-Rich Plasma (PRP) - Pure Platelet-Rich Plasma (P-PRP) or Leukocyte- and Platelet-Rich Plasma (L-PRP) - but still limited about Platelet-Rich Fibrin (PRF) subfamilies. In this second article, we describe and discuss the current published knowledge about the use of PRP and PRF during implant placement (particularly as surface treatment for the stimulation of osseointegration), the treatment of peri-implant bone defects (after peri-implantitis, during implantation in an insufficient bone volume or during immediate post-extraction or post-avulsion implantation), the sinus-lift procedures and various complex implant-supported treatments. Other potential applications of the platelet concentrates are also highlighted in maxillofacial reconstructive surgery, for the treatment of patients using bisphosphonates, anticoagulants or with post-tumoral irradiated maxilla. Finally, we particularly insist on the perspectives in this field, through the description and illustration of the use of L-PRF (Leukocyte- and Platelet-Rich Fibrin) clots and membranes during the regeneration of peri-implant bone defects, during the sinus-lift procedure and during complex implant-supported rehabilitations. The use of L-PRF allowed to define a new therapeutic concept called the Natural Bone Regeneration (NBR) for the reconstruction of the alveolar ridges at the gingival and bone levels. As it is illustrated in this article, the NBR principles allow to push away some technical limits of global implant-supported rehabilitations, particularly when combined with other powerful biotechnological tools: metronidazole solution, adequate bone substitutes and improved implant designs and surfaces (for example here AstraTech Osseospeed or Intra-Lock Ossean implants). As a general conclusion, we are currently living a transition period in the use of PRP and PRF in oral and maxillofacial surgery. PRPs failed to prove strong strategic advantages that could justify their use in daily practice, and the use of most PRP techniques will probably be limited to some very specific applications where satisfactory results have been reached. Only a few simple, inexpensive and efficient techniques such as the L-PRF will continue to develop in oral and maxillofacial surgery in the next years. This natural evolution illustrates that clinical sciences need concrete and practical solutions, and not hypothetical benefits. The history of platelet concentrates in oral and maxillofacial surgery finally demonstrates also how the techniques evolve and sometimes promote the definition of new therapeutical concepts and clinical protocols in the today's era of regenerative medicine.

Keywords: Blood platelet, fibrin, growth factors, leukocytes, oral surgery, dental implants, platelet-rich fibrin (PRF), platelet-rich plasma (PRP), regenerative medicine, tissue engineering.

1. PLATELET CONCENTRATES IN ORAL AND MAXILLOFACIAL SURGERY: AN IMPLANT AND SINUS-LIFT STORY

As previously explained in the first part of this article, the history of platelet concentrates was intimately related to oral and maxillofacial surgery, and an incredible volume of articles has been published about PRP (Platelet-Rich Plasma) and PRF (Platelet-Rich Fibrin) in this field. Even if the history of platelet-rich healing preparations started a long time before in plastic surgery [1-3], the craze for growth factors was launched because of two articles about the use of PRP/platelet gels in maxillofacial applications [4] and particularly the use of the platelet gel for the improvement of large bone grafts [5]. In fact, bone grafting was and remains the main field of evaluation of the effects of platelet concentrates, and in the literature, no application was more tested with platelet concentrates than the sinus-lift procedure. This situation can be explained easily by economic considerations: the craze for platelet concentrate technologies required

*Address correspondence to this author at the LoB5 Unit, Chonnam National University School of Dentistry, 77 Yongbong-Ro, Buk-Gu, Gwangju 500-757, South Korea; E-mail: LoB5@mac.com

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the development of protocols, kits and devices usable in daily practice, and such a development was only possible if companies could find a significant market for these products [6, 7]. The dental field in general (and the implant and preimplant surgery in particular) represented an enormous market, with a higher number of surgical acts per year than any other clinical discipline and therefore with the highest potential consumption of single-use kits and devices.

If platelet concentrates could be used in most maxillofacial surgical procedures, the field of preimplant bone graft and dental implant seemed the perfect commercial target for these technologies, since clinicians are always looking for adjuvants that may increase soft tissue healing and bone regeneration. The improvement and acceleration of the bone graft integration is of particular interest when dental implants have to be inserted in the grafted volume, in order to reduce the time before implant placement and to increase their stability [8]. Moreover, the healing of a bone graft is also dependent on an adequate soft tissue wound closure, for which platelet concentrates (like fibrin glues)[9, 10] are particularly efficient: historically, the very first platelet-fibrinogen preparations were used as fibrin sealants for soft tissues [11-14]. Finally, the platelet concentrates technologies allow to collect only a quite small volume of product, and small surgical sites were thus naturally indicated for the use of these preparations: preimplant bone graft and implant dentistry therefore fit the intrinsic characteristics of these platelet-fibrin gels, and many companies developed their specific kits and protocols for these applications [7].

Since sinus-lift is one of the most frequent bone graft procedure in implant dentistry, it became one of the most investigated procedures with platelet concentrates. Another reason is that sinus-lift is a very good healing model for the evaluation of bone remodelling: it is a closed and protected cavity where the interferences with oral environment and maxillomandibular functions are minimal; the bone healing can therefore be evaluated with minimal bias.

Unfortunately, the published data about platelet concentrates and bone healing in general [15], and during sinus-lift in particular [8], are contradictory. The lack of an adequate terminology and the absence of characterization of the tested platelet concentrates (particularly concerning the leukocyte content and fibrin architecture) make the accurate critical review of the published data very difficult [7], and the explanations of the controversial results remain often uncertain. Moreover, the commercial interests behind the development of the various platelet concentrate technologies may obscure the lack of true potential benefits in some cases [16]. Finally, like in all trends, the personal convictions of some researchers (and often their lack of knowledge about blood coagulation) may also contribute to obscure the correct evaluation of the clinical results observed with platelet concentrates: some authors were « for PRPs » while others were « against PRP ». If hypothesis-driven studies are necessary for the definition of adequate materials and methods, certainty-driven studies are always leading to a distortion of our knowledge. For all these reasons, the large literature on the topic remains a blind library of knowledge.

The review of the current knowledge about PRP and PRF for bone graft, implant and reconstructive maxillofacial surgery is therefore a challenge, that requires to consider the published data with caution. Sinus-lift and implant dentistry were historically linked to these technologies, and remained the major applications tested in maxillofacial surgery: a critical review of these data can therefore lead our reflexion about the general impact of these products and the perspectives of platelet concentrates in this field. However, many other aspects than bone healing must also be taken into consideration and are discussed in this article.

2. DO PRP AND PRF STIMULATE BONE REGENERATION?

One of the most important unsolved question in the literature about platelet concentrate is to understand if these preparations can improve or accelerate bone healing and remodelling. The answer is still very complex, and the analysis of the literature does not give a clear answer. Two observations could however lead our reflexion. First, the literature about various forms of PRP is large and contradictory, while the limited literature about PRF is more recent and homogeneous [7]. Second, in most studies about bone healing with PRPs, it is difficult to determine what kind of PRP was used: Pure Platelet-Rich Plasma (P-PRP) or Leukocyte- and Platelet-Rich Plasma (L-PRP)? On the contrary, most studies with PRF were performed with L-PRF (Leukocyte- and Platelet-Rich Fibrin) [17].

2.1. PRP and Bone Regeneration

As previously explained in the first part of this article, the *in vitro* cell data are quite contradictory with PRP. As a whole, PRPs are considered to increase the proliferation of osteoblasts in various cell models [18-22], even if the contrary was also proven [23, 24], while their effects on differentiation are dependent on the culture conditions [18, 20, 22]. Even if the *in vitro* mechanisms are far from being understood in details, the effects of PRP on cells in culture are also deeply modulated by the type of bone graft biomaterial used in combination [25]. The questionings concerning the effects of PRPs on bone healing are then difficult to answer, since they are deeply interlinked with the nature of the supporting bone biomaterial, which can be of many different kinds: autologous (iliac, calvaria, chin, retromolar,…), xenogeneic (bovine, porcine, equine,…), allogeneic (freeze-dried bone allograft (FDBA), demineralized freeze-dried bone allograft (DFDBA),…), or synthetic (beta tricalcium phosphate (βTCP), hydroxyapatite,…). Potential combinations of the various PRPs with the various bone materials are numerous, and the evaluation of their clinical results may seem an endless task [26].

Many *in vivo* data were collected in various animal models (rat, rabbit, dog, pig, goat) with various PRPs alone or in association with various bone biomaterials. Some authors concluded that PRP gels have no impact on bone regeneration alone [27, 28] or in association with autologous bone graft [28-32], allograft [33-35], xenograft (such as anorganic bovine bone)[36] or synthetic materials (such as βTCP)[37]. On the contrary, other authors concluded that these PRP gels stimulate significantly bone healing in association with autologous bone [38-42], allograft [43], xenograft (such as anorganic bovine bone)[44, 45], synthetic materials (such as

βTCP) [46] or a combination of different materials [47]. The results seemed therefore exactly contradictory.

In order to explain some of these data, some authors hypothesized that the beneficial effects of PRPs associated with autologous bone graft were only observable during the early phases of healing, for example during the first month in a dog model [48, 49] or in a rabbit model [50], and that these effects were no more significant on a longer term basis, when the natural bone healing had reached a certain level of maturation. Similar explanation was developed for the combination of PRP with βTCP in a dog model, where a significant effect on bone healing was assessed up to 3 months, but was no more observable after 6 months [46]. However, on the contrary, some authors did not find any significant effects of PRPs on autologous bone graft even during the early healing after 2 to 8 weeks in rabbit models [28, 29, 31] and from 2 to 12 weeks in a swine model [32]. Another explanation was that there may be an optimal proportion for the mixture of PRP with the various bone biomaterials in order to get the best clinical results [51]. This parameter may be relevant in some specific clinical applications, however it remains an experimental concept, both theoretical and difficult to control in clinical practice on a bleeding surgical site; moreover, without a careful evaluation of the fibrin architecture and the platelet/leukocyte content of the platelet concentrate, discussions about the ideal bone biomaterial/PRP ratio are pointless.

A last approach gave excellent consensual results: the combination of PRP with various biomaterials (allograft, fluorohydroxyapatite,…) [52, 53] and bone mesenchymal stem cells (BMSC). This tissue engineering approach requires to use the PRP gel as a cell-supporting medium and matrix for the BMSC. Fibrin gels or glues historically gave excellent results as supporting matrix for tissue engineering [54], and PRPs were logically beneficial in these applications. This *in vitro* biotechnological approach remains however far from the daily clinical reality, and does not really answer to the question of the effects of PRPs on natural bone healing.

As a whole, the data published with many different PRP gels and bone substitutes in various animal models are difficult to sort and interpret, and it is difficult to draw legitimate conclusions from all these studies. The reasons are multiple: lack of characterization of the tested PRPs, animal models with coagulation and healing kinetics too far from the human, or even animal models that do not allow to produce adequately some PRP gels [55]. Indeed, animal models are always different from human biology, and the limits of the models become critical with PRPs. Platelet concentrates are autologous blood products and their biology is dependent on the species: PRPs are therefore not the same products between animals and humans. This obvious statement probably explains the great contradictory results described in the literature, where for example some authors pointed out in a study that rat and goat PRPs had no effect on bone formation, while human PRP improved the initial osteogenic response of human bone graft [56]. Moreover, in all studies, the exact nature of the tested PRPs was undetermined, and this is a critical issue since the various PRP protocols designed for human blood do not necessarily lead to the same products in the various animal species. The leukocyte content was almost never assessed, the leukocyte formula was unknown and probably uncontrolled, the platelet concentration itself was often unclear, even if these parameters have a considerable impact in biomaterial research: obviously, a concentration of macrophages does not have the same impact than an overpopulation of lymphocytes [57], particularly with some bone substitutes that can be naturally immunogenic [58, 59]. A last important bias is interspecies interference: for example, when authors are testing allograft, one should remember that what is an allograft for a human is in fact a xenograft for an animal. And we have no idea of the interactions between a xenograft of a species (such as bovine bone) with another species (for example a dog surgical model).

Even if the level of proof of the literature about PRPs in animal models seems weak, it is possible to extrapolate and determine the true impact of PRP on bone healing. As it was discussed in the first part of this article, natural bone healing is first of all dependent on the blood coagulation, the fibrin/platelet matrix being the first support of cell proliferation and differentiation. Since PRPs have to be considered as improved fibrin glues, their effects on bone healing are finally more dependent on the way the materials are used than on direct and automatic bone healing properties. These products are only good supporting materials for a natural osteogenic process, but there are no miracles to expect. This was well illustrated by the study of Plachokova *et al.* [56] that concluded that human PRP combined with human bone graft had better osteogenic capacity than human PRP combined with synthetic bone substitute: the PRPs may stimulate the cells of an autologous graft, but what happens when there are no cells in the grafted bone biomaterials? The stimulation of healing is then only indirect, since there are no bone cells to stimulate directly. This result was therefore very logical.

There are therefore several different answers to the questionings about the biological effects of the various PRPs on bone healing. Most animal studies were very experimental, and did not try to understand the clinical reality. In human clinic, direct bone healing properties are not the sole parameters: the problem is also to secure complex surgical procedures and to improve the esthetic and functional outcomes. The problem is thus not only quantitative but also qualitative: the question is not the volume of regenerated bone but how the tissues (bone and soft tissue) heal. For all these reasons, the use of PRPs should be discussed in various clinical situations and not in animal theoretical models. This also implies to consider technical and economic aspects, since PRPs are expensive and time-consuming techniques, but also allow an efficient handling of the bone graft biomaterial during surgical procedures through the setting of the bone material within the PRP fibrin gel. The true question is therefore not to know if the various PRPs stimulate bone healing in a theoretical model, but to determine if the advantages of these techniques are superior to their inconvenients and may truly help to obtain better results than the same techniques without PRPs in human clinic.

2.2. L-PRF and Bone Regeneration

The literature about L-PRF and bone healing is more homogeneous. It was shown that the L-PRF clot stimulates

in vitro the proliferation and the differentiation of osteoblasts [60] and BMSCs [61]. These stimulations were dose-dependent, and the role of the leukocytes in the proliferation/differentiation profiles was pointed out. This homogeneous stimulation was probably related to the slow release of growth factors and other blood molecules during more than 7 days [62-65]. Similar stimulations were observed in other cell models testing only the clot exudate (and therefore without contact with the fibrin matrix and its cell content)[66, 67]. Even if the results about bone healing were always positive, the number of animal studies with L-PRF remains very limited [68, 69], because it is impossible to produce a correct L-PRF clot in small animal models (rat, rabbit)[55]. However, two series of human clinical studies allowed us to understand the effects of the L-PRF in bone regeneration. First, during sinus-lift procedures, it was shown that the filling of the subsinus cavity with L-PRF clots only, allowed the full bone regeneration of the cavity [70, 71]; even if similar treatments using the natural blood clot as sole filling material could also promote partial bone regeneration [72-75], the results with L-PRF were much stronger and secure. Second, the combination of L-PRF with allograft during sinus-lift and lateral grafting of the alveolar ridges also promoted more secure, quick and high quality bone regeneration [76] and implant-supported rehabilitation [77, 78] than the same treatments without L-PRF.

These human clinical results illustrated how the L-PRF can influence bone healing. In the classical technique, L-PRF is a natural optimized blood clot [79]: it is the solid form of blood after coagulation, assembled in an homogeneous and strong fibrin matrix, without red blood cells (RBC) but with all the other actors of the circulating tissue (platelets, leukocytes, circulating stem cells). The main difference with a natural blood clot is that L-PRF is very stable and homogeneous since it was prepared outside the surgical site, and this biomaterial is therefore very easy to handle and to place at the right moment at the right place. Usually, clinicians have a limited control on the natural bleeding and clotting; with L-PRF, the surgeons take the control over the blood clot and can control and therefore improve the early phases of healing. Logically, since natural bleeding is the key of an efficient bone healing, the use of optimized blood clots can improve the natural healing process, alone or in association with a bone substitute. The main issue is then to define clinical protocols to obtain the best esthetic and functional outcomes.

As a first conclusion, the literature does not allow to draw definitive conclusions on the various PRPs and L-PRF and the best way to use them for bone healing in oral and maxillofacial surgery. The various kinds of PRP can mainly be used as soft fibrin gels mixed with a bone graft material or placed above a grafted volume in order to support and stimulate tissue healing; if beneficial effects are expected, PRP gels did not change the way surgical procedures were performed, PRP gels remained surgical adjuvants for the potential improvement of bone and soft tissue healing. On the contrary, the specific form of L-PRF opened a new range of surgical procedures that could not be expected without L-PRF; the L-PRF membranes and clots present indeed strong mechanical and biological properties that allowed to define completely new therapeutic approaches. For sure, the concepts described in the first part of this article can be extended to many other clinical situations: this is particularly true for NBR (Natural Bone Regeneration), which is also a key therapeutic concept in implant dentistry. The use of L-PRF is in fact a tissue manipulation through the transformation of blood into a natural biomaterial, and then its use for *in vivo* tissue engineering applications. Finally, the L-PRF technique is simple, quick and inexpensive and therefore completely fits a daily clinical practice. For all these reasons, this article describes the published data about the various forms of PRPs, but particularly develops the clinical concepts associated with the use of L-PRF. As it was discussed in the first part of this article about periodontology and oral surgery, we can expect that on a long term basis L-PRF will remain the main (and even maybe the sole) platelet concentrate technique used in maxillofacial surgery, and particularly bone graft and implant-supported rehabilitation.

3. PRP AND PRF ON IMPLANT SURFACES, OR THE DREAM OF BOOSTING THE OSSEOINTEGRATION

In implant dentistry, the development of optimized implant surfaces is currently an intensive field of research [80-83]. The purpose of these works is to reinforce and accelerate the osseointegration process of the implant surface: consequently, the waiting period before the secure function of the implants could be reduced and the immediate loading of the implants could be more secure. Most dental implants are made in titanium, and the process of osseointegration is based on the bone apposition on the titanium dioxide TiO_2 superficial layer of the surface [82]. In order to improve the osseointegration and the bone anchorage, the main surface modifications are chemical and/or physical [84]. Chemistry modification of the TiO_2 layer (such as the impregnation with calcium phosphate CaP or fluoride for example)[85, 86] can improve the osseointegration through the acceleration of precipitation of mineral ions on the surface or the direct modulation of the cell activity on the surface [86, 87]. On the other hand, physical modifications are related to the topography of the surface at the micrometer [88] and nanometer scales [89]: an adequate microtopography can increase the developed area of the bone/surface interface and therefore improve their biomechanical interlocking [80], while a well-designed nanotopography can increase the adsorption of blood and matrix proteins on the surface and even directly influence the bone cells proliferation and differentiation [84].

Osseointegration is thus first of all dependent on physico-chemical parameters, and the associated biological mechanisms are only a consequence of the surface chemistry and texture. During implant placement, the implant surface is covered with blood, and the coagulation on the surface immediately creates a thick fibrin-platelet layer [90]. Blood remains the first matrix of healing during osseointegration, but only a small layer of blood is required to fullfill this initial biological function. The artificial addition of some more platelet or growth factors from a PRP on the surface should logically not significantly modify the architecture of the initial blood layer in the early phases of healing, not influence the chemico-physical interactions between the implant and the bone tissue on a longer term, and thus not interfere with the osseointegration process in general. Moreover it was proven that the dense clotting of platelets and fibrin on the

surface was 1000 times stronger with whole blood than with PRP suspensions [91]: during coagulation, all the blood components have specific functions, and PRP suspensions are only incomplete imitations of blood ; PRP suspensions are therefore less biologically active than the natural bleeding for the blood coating of an implant surface.

For all these reasons, the use of platelet concentrates for the acceleration of osseointegration does not seem the most logical approach, particularly nowadays with high-tech surfaces presenting improved chemical and physical properties. However, some authors tried to assess the effects of some platelet suspensions on the osseointegration of dental implants. Several studies were performed with the PRGF technique (Plasma [92] or Preparation Rich in Growth Factors [93], BTI, Vitoria, Spain). This is a manual protocol for the production of a P-PRP suspension [7] with a lower platelet concentration in comparison to other PRPs [94]. Anitua and coauthors showed in a goat model that the coating of their titanium implants with PRGF increased the bone regeneration and the osseointegration of their implants during the early phases of healing [95]. In a 5 year retrospective study, these authors also reported their clinical experience [96], after conditioning the implant surface with PRGF before implant placement and immediate loading, with good but quite common clinical results. The main issue is that most of these data about PRGF were provided by the company marketing the PRGF technology and the associated implants: BTI, aka Biotechnology Institute, is a dental implant company, and Anitua *et al*. unfortunately often forgot to disclose their enormous commercial interest in most of their publications about this technique [16]. Therefore, the credibility of these works is debatable.

A few other articles supported the idea that the conditioning of the implant surface with a PRP solution could improve osseointegration in some experimental models [97, 98], but on the contrary, most other independent studies showed that the coating of the implant surface with PRP or the conditioning with PRP of the implant osteotomy chamber before implant placement did not lead to any beneficial effects in terms of osseointegration [99-103], even if a transitory small improvement of bone healing was suspected during the early phases of healing only [104, 105]. Some authors also showed that the conditioning with PRP can even have a negative impact of osseointegration in some conditions [100, 101] ; indeed, if the addition of some more platelets may not stimulate the general process of osseointegration, an excessive amount of platelets and PRP on the surface may on the contrary disturb the osseointegration process and lead to inhibitory effects. Finally, the potential effects of PRP-conditioning may also be dependent on the type of surface. Indeed two studies showed that the same PRP can improve the early healing of basic titanium implants without surface modification and have strictly no effect on the osseointegration of implants with chemical modifications [102, 103]. Therefore, conditioning with PRP may be beneficial only for surfaces that are not already improved, and this may explain the good results published by the BTI dental implant company with their own implant system and surface.

From all these data, it is impossible to draw extensive scientific conclusions: the many experimental models are difficult to extrapolate to human clinics, the exact content of the various tested PRPs is unknown, conflicts of interest were also reported. There is however one last key parameter to take into consideration when considering the relevance of this specific clinical application of platelet concentrates: PRPs are expensive and time-consuming techniques. It seems therefore completely pointless in daily practice to prepare a PRP for the coating of an implant surface before implant placement, considering that the success rate of high quality implants is above 96% with the standard procedure without PRP [106, 107], and that high-performance surfaces are available on the market and lead to higher bone anchorage [81, 82, 84, 108]. Surface coating with PRP is clearly not the easiest and most efficient approach to improve implant surfaces.

Moreover, the so-called « bioactivation » of the surface with a PRP suspension [96] can not be considered as a true surface modification on a long term basis. Indeed, when some slight beneficial effects of PRP coating were observed on osseointegration, these effects were always transitory and limited to early healing [104, 105]. On a longer term, PRP coating had no effect on the osseointegration, and this result is quite normal since the bone regeneration on the surface quickly reached a plateau, related to the maximum bone/implant contact on the surface. On a longer term, only the intrinsic chemical and physical characteristics of the surface can truly increase the bone anchorage, such as an optimal microroughness (for biomechanical interlocking) and a thick and stable TiO_2 layer (for chemical interlocking)[80, 81, 84]. The selection of an efficient implant system seems a better approach than the manual preparation of home-made PRP-coated surfaces, in order to get the best results on a short and long term.

As a conclusion, in comparison to modern surface engineering based of chemistry and topographical modifications, the conditioning of the implant surface with platelet suspensions seems a dead-end technological concept. This is the sole pragmatic conclusion.

4. PRP AND PRF FOR THE REGENERATION OF PERI-IMPLANT BONE DEFECTS

Platelet concentrates may not be relevant to improve osseointegration in normal conditions, but they may help for the regeneration of peri-implant bone defects. Three specific situations can be encountered.

The first kinds of peri-implant bone defects are the consequences of the pathology of osseointegration, the peri-implantitis, also called deosseointegration [109]. The triggering mechanisms of peri-implantitis are often considered to be the bacterial contamination or a mechanical overload of the implant with parasitic or excessive mechanical forces ; however, even if many parameters influence the development of this pathology, the biological mechanisms of peri-implantitis are in fact mainly related to bone/implant interface breakdown and surface chemistry modification. Once the titanium dioxide layer is compromised and contaminated, the reconstitution of a stable titanium dioxide layer is almost impossible without the use of an adapted methodology of surface reconditioning [109].

The second kinds of peri-implant bone defects are provoked during implant placement, when the initial bone volume for implantation is not large enough for the support of implants. Some area of the implant (particularly the collar and the first threads) can not be placed in the bone, or lateral perforations of the bone ridges may occur. It is then important to graft some bone on these areas in order to reinforce the bone anchorage of the implant, but also to protect the implant from soft tissue invagination. In implant dentistry, the covering of these uncovered implant surface area is necessary for esthetic and functional rehabilitations, since gingival dehiscences around the implant can severely compromise the esthetic result and the long-term stability of the implant-supported treatment, with an increasing risk of peri-implantitis.

The last kinds of peri-implant bone defects can be encountered during an immediate post-avulsion or post-extraction [110] implantation procedure. When an implant is placed in a fresh avulsion socket, the drilling of the implant cavity allows to block the implant in the bone, but the natural shape of the alveolar socket does not follow the cylinder or cylindro-conical shape of the implant; large peri-implant defects must then be filled with a material in order to promote bone regeneration around the implant and to avoid soft tissue invagination. The final purpose of this filling is both functional and esthetic: the bone regeneration will hopefully promote osseointegration of the implant surface and maintain the soft tissue above for a healthy and natural peri-implant gingiva.

In these 3 applications, it is important to understand that 2 separate objectives are at stake. The first objective is the bone regeneration inside the defect, i.e. the formation of a new bone tissue to fill the peri-implant cavity: the mechanism is only related to bone biology and the osteogenic properties of the various filling materials. The second objective is the reosseointegration of the surface, i.e. the reconstitution of the bone/implant interface: the mechanism is then mainly a physico-chemical interaction between bone and the titanium dioxide surface. Understanding these different principles is necessary for the review of the numerous studies about the impact of various PRPs in these applications, but also for the definition of new efficient therapeutic strategies, particularly NBR with L-PRF.

4.1. PRPs and Peri-Implant Bone Defects

The use of PRP gels, alone or in addition to a bone material for the filling of peri-implant defects, was naturally tested in many different situations and in association with many different bone substitutes and techniques. Like in most articles in this field, the data are debatable since the content of the tested PRPs is always unknown and the animal models are far from the human reality. The results are however quite homogeneous.

In various dog models, most authors did not find any beneficial effects of PRP alone [111, 112] or in combination with xenogeneic bone graft [113-115] during the filling of artificial peri-implant bone defects, even when GBR (Guided Bone Regeneration) membranes were used for the protection of the PRP [112]. Some authors even showed a negative effect of PRP on the healing of the bone defects filled with a xenogeneic bone biomaterial [116]. Only a few authors reported a positive impact of the addition of PRP to a bone substitute (xenogeneic bone or particulate dentin-plaster of Paris) during the filling of peri-implant bone defects [117, 118], but these positive results are quite isolated.

As a whole, the literature about the use of PRP during the treatment of peri-implant bone defects did not highlight any beneficial effects of PRP, whatever the kinds of defects. The explanation is probably quite simple: PRPs are blood extracts, and the natural bleeding on the surgical site in the peri-implant bone defects is probably sufficient to saturate the filling bone materials with fibrin and platelets; the addition of some more platelets from a PRP gel did not significantly change the healing equation. Moreover, as it was explained in the previous chapter, osseointegration is mainly a physico-chemical interface mechanism where a natural bleeding is enough for the initial coating of the surface with fibrin and platelets.

However, further thought needs to be given to the concept of platelet concentrate for peri-implant bone regeneration. First, a few studies showed that some biotechnological approaches may offer much more satisfactory results, particularly the use of bone mesenchymal stem cells [119] or periosteum membranes [120] cultivated with a PRP gel as supporting biomaterial. This approach is obviously too complicated for daily clinical practice, but these experiments support the concept of *in vivo* tissue engineering. Second, a few studies showed that the association of PRP with a dense fibrin matrix was necessary to obtain the best possible clinical results during the treatment of peri-implant bone defects [119, 121]: for example, the treatment of peri-implant defects with platelet-enriched fibrin glue promoted a greater bone-implant contact and a stronger peri-implant bone healing than with PRP [121]. Therefore, if PRPs are not very relevant as surgical adjuvants for the treatment of peri-implant defects, L-PRF may be on the contrary efficient and offer some new therapeutic opportunities.

4.2. L-PRF and NBR to Regenerate Peri-Implant Bone Defects

As it was already discussed in the first part of this article, L-PRF is a solid fibrin biomaterial [79], and not a platelet suspension or a light fibrin gel like the PRPs [7]. A L-PRF membrane contains most platelets and at least half of the leukocytes (particularly the lymphocytes) collected in the 9mL blood harvest [79]. The L-PRF clot is produced without blood modification and is the consequence of the natural coagulation of blood during centrifugation [6, 122-124]. With its strong fibrin architecture and specific 3D cell distribution (leukocytes, platelet aggregates, ciculating stem cells), the L-PRF clot is in fact an optimized blood clot. As it was shown that a dense fibrin matrix was necessary to obtain a beneficial effect with PRP in these treatments [119, 121], L-PRF may therefore offer positive results when used in combination with bone biomaterials for the filling of peri-implant bone defects. However, the specific architecture of L-PRF also allows to define new therapeutic approaches. L-PRF can indeed be mixed with a bone graft (like a PRP), but also used as a strong regeneration membrane to cover the bone regenerative area and to stimulate soft tissue healing.

This concept of *in vivo* tissue engineering was already described in the first part of this article and was called the Natural Bone Regeneration (NBR). If NBR is efficient for the regeneration of post-avulsion sockets, this therapeutic concept can be successfully extended to many other clinical situations and be efficient for the regeneration of peri-implant defects. There are still only few studies published in the international literature about the use of L-PRF in peri-implant bone defects [68], and we will therefore illustrate the NBR concept with our 8-years long clinical experience [125, 126].

The general concept of NBR is to promote the simultaneous regeneration of a bone volume and the gingival tissue above through the use of L-PRF membranes. L-PRF can be used as filling material within the bone regenerative chamber, most times in association with a bone material used as space maintainer, and also as protection membrane above the bone regenerative compartment [77, 78]. The covering L-PRF layers also stimulate the soft tissue healing and promote the induction of the gingival remodelling [127, 128]. This approach is based on the intrinsic polyvalent properties of the L-PRF membranes, particularly their effects on proliferation and differentiation of bone and gingival cell populations [60]. In the NBR process, the L-PRF membranes stimulate both bone and gingival compartments, particularly through the long-term slow relase of growth factors and matrix proteins [62]. The L-PRF layer also constitutes the new interface between both compartments, and regulates the interactions between bone and the covering soft tissue, in order to promote a synchronized healing and remodelling of the various tissues of the alveolar ridge. Finally, the NBR is often combined with a metronidazole solution soaking the filling material in order to protect the bone healing compartment from the unavoidable bacterial contaminations [129].

NBR seems a relevant alternative to the other methods used for the treatment of peri-implant bone defects, mainly bone graft and GBR (Guided Bone Regeneration). Bone graft can give satisfactory results on bone healing but has no impact on soft tissue healing and may be compromised by local infection and inflammation. The use of GBR membranes such as non resorbable ePTFE (expanded polytetrafluoroethylene) or resorbable collagen membranes is a good method to protect the bone compartment, but these membranes have a negative impact on soft tissue healing and even increase the risk of gingival dehiscence, contamination of the grafted site and the associated bone and flap necrosis. This comparison between GBR and NBR was already widely discussed in the first part of this article, and the same arguments can be used here. NBR is clearly a simple and efficient therapeutic alternative. The strategies of NBR are however dependent on the kind of peri-implant bone defect to treat.

First, for the treatment of defects related to peri-implantitis, the classical NBR may not be efficient alone. Indeed, as it was previously explained, peri-implantitis is first of all a pathology of osseointegration dependent on physico-chemical surface parameters. A peri-implantitis is always an infected and inflammatory defect, and the uncovered implant surface is completely contaminated with infectious pollutions and has lost its physico-chemical characteristics. The surface TiO_2 layer is destroyed and the possibility to restore a clean TiO_2 layer is highly compromised. Theoretically, the reosseointegration of a contaminated surface requires the complete cleaning and the reconditioning of the TiO_2 layer; one suggested protocol was to clean the surface with laser burning and citric acid rinsing, and then to use the decomposition of hydrogen peroxide solution (H_2O_2) with a laser heating in order to reconstitute a chemically-intact TiO_2 superficial layer [109]. Following these principles, the cleaning of the compromised surface and the filling of the peri-implant defects with L-PRF and bone materials could logically not induce the complete recover of the osseointegration, as long as the surface chemico-physical aspects were not restored. However, from our experience using NBR principles with L-PRF and allograft associated with a 0.5% metronidazole solution [129], the use of NBR around compromised surfaces promoted the complete healing of severe peri-implantitis defects. The impact of the metronidazole solution should not be neglected in the local decontamination of the surface. However, our experience is limited since we mainly use 2 high quality implant systems with improved surfaces (Osseospeed, AstraTech, Mölndal, Sweden and Ossean, Intra-Lock, Boca-Raton, Florida, USA)[85, 86] with a very small number of cases of peri-implantitis. Moreover, these 2 surfaces present a moderate roughness and the consequences of the peri-implantitis surface pollutions may be easier to treat in these surfaces than in other systems. For example, peri-implantitis on anodized surfaces are much more difficult to treat, because they are often associated to extended cracks of the TiO_2 superficial layer [84] and deep contaminations in the crevices [109]. Logically, the kind of surface may considerably influence the clinical outcome of the treatment of peri-implantitis, even with the help of L-PRF and metronidazole. It is therefore difficult to extend our positive clinical results to all configurations. Finally, NBR is very efficient for the regeneration of peri-implantitis bone defects, but the impact of NBR techniques on the reosseointegration process is more uncertain and requires further evaluation.

Second, when the alveolar ridge is not large enough for the complete insertion of the implants, the NBR protocol can promote a full bone reconstruction over the uncovered parts of the implants (most time the collar and some threads). In this clinical situation Fig. (**1**), the main issue is not the osseointegration of the implant surface (the surface is clean and there is no reason to fear pollutions and lack of osseointegration) but the protection of the bone regenerative chamber. Indeed, implants are stabilized in the residual bone volume and the bone defect has often one wall only: the bone grafting material is therefore difficult to stabilize around the implant. Moreover, the gingival tissue is not very extensible and the addition of a significant volume of bone grafting material requires to pull up the gingival flap above the grafted volume. These problems remained difficult to solve with classical bone grafting or GBR, but on the contrary, a classical NBR can treat these defects easily. During NBR, the bone compartment is filled with a mix of L-PRF and hard bone biomaterial (used as space maintainer) and covered with several L-PRF layers Fig. (**1**). During the sutures, the flaps are pulled up above the bone graft; if tight sutures are not possible, it is not a problem if sufficient L-PRF layers are

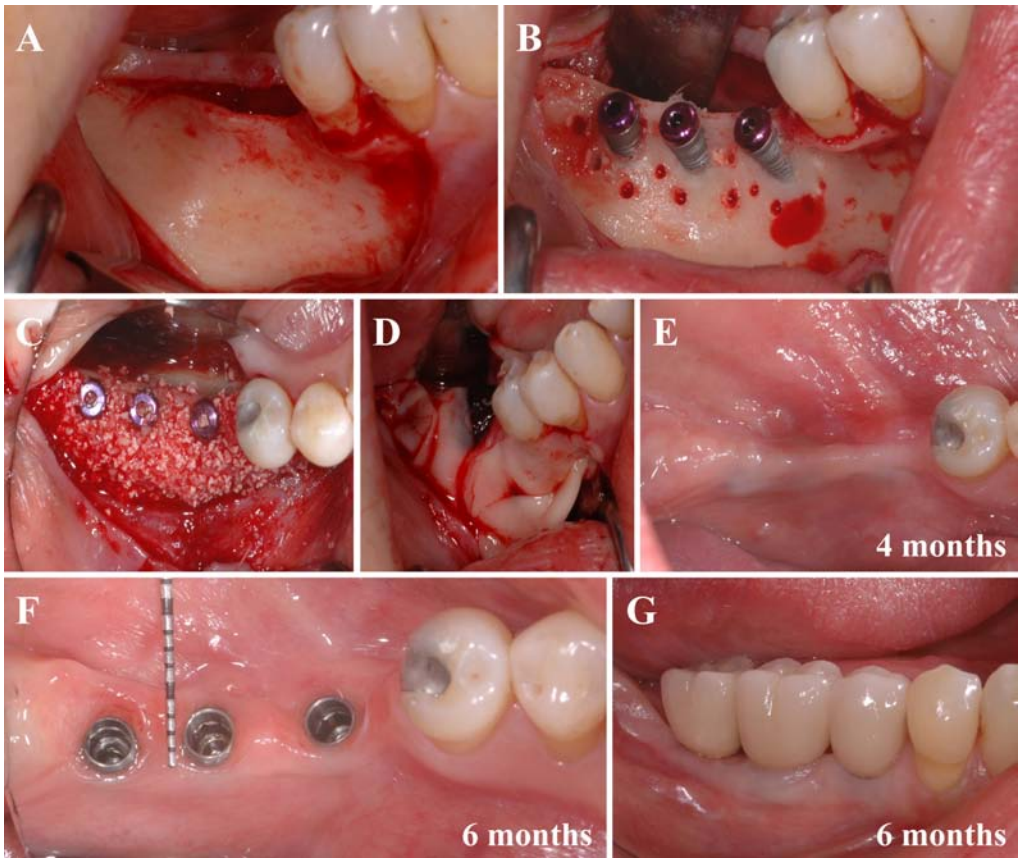

Fig. (1). Natural Bone Regeneration (NBR) with xenograft of peri-implant bone defects created during implant placement in a thin resorbed alveolar ridge. **A.** The mandibular posterior alveolar ridge was very thin, and the bone volume was not sufficient for a correct implant placement. **B.** After implantation, the vestibular faces of the 3 implants (Ossean, Intra-Lock, Boca-Raton, Florida) remained uncovered, resulting in a lower bone anchorage and a serious risk of tissue dehiscences around the implants on a short-term basis. The implants were only blocked by the tip in the bone. The first step of the NBR procedure was to perforate the vestibular cortical bone more than 10 times with a small drill, in order to promote local bone bleeding (endosseous stimulation). **C.** The vestibular face of the alveolar ridge was then grafted with a mix of L-PRF and xenogeneic collagenated bone (Gen-Os, OsteoBiol, Tecnoss, Italy) in a 50/50 volumic ratio, in association with a 0.5% metronidazole solution. The uncovered threads of the implants were covered, and a significant grafting volume was added in order to regenerate a broad alveolar ridge around the implants. **D.** Following the NBR principles, several L-PRF layers were added on the grafted area in order to protect the bone material and to stimulate periosteum and soft tissue healing and remodelling. **E.** Four months after surgery, the keratinized gingival tissue above the implants seemed thick and strong, and the transgingival healing screws could be connected. **F** and **G.** Six months after surgery, the healing screws were removed and the final prosthetic restoration was built. The regenerated alveolar ridge was finally quite broad and the gingival tissues were thick and healthy, without dehiscence around the implants. Both bone and soft tissues compartments were regenerated simultaneously by the NBR procedure: this is the synchronized regeneration principle.

used above the grafted volume, since the L-PRF cover can protect the surgical site from the oral environment and promote the quick cell proliferation and migration, re-epithelialization and wound closure. The bone compartment is therefore sufficiently protected. Moreover, in all cases, the L-PRF promotes the formation of a thick gingival tissue above the bone compartment, through several phases which were already described in mucogingival surgery: immediate induction of a new development pattern through the slow release of growth factors and matrix proteins, the slow merging of the fibrin matrix with the connective tissue and periosteum, and the remodelling of the gingiva on a longer term basis. The high quality of the peri-implant gingival tissue is however not only related to the healing on L-PRF membranes but is also linked to the bone regeneration below: a sufficient peri-implant bone support is necessary for the remodelling of a healthy gingival tissue, and this equation reinforces the principles of NBR, where the regenerations of the bone and gingival compartments are interrelated and synchronized. Finally, in this application, the clinical results of NBR for the restoration of the peri-implant bone and gingival volumes are very satisfactory from a mechanical and esthetic standpoint Fig. (**1**). However, the procedure can probably be improved by the combination of NBR with some specific adjuvants (such as metronidazole for the protection of the grafted volume from the unavoidable oral bacterial contaminations) and the use of the adequate bone substitute to associate with the L-PRF membranes. As it was already discussed in the first part of this article about NBR after dental avulsion, it is still necessary to investigate and validate the numerous potential clinical protocols and associated materials, even if the NBR concepts are very efficient.

Third, the use of NBR for the regeneration of peri-implant defects after immediate post-avulsion implantation is also a simple and efficient option Fig. (**2**) [125, 126]. In this specific application, the peri-implant defects are often quite small, and the addition of L-PRF to a bone biomaterial for the filling of these defects may be of minor interest for bone healing if the surgical site is clean. However, there are several key advantages in the use of L-PRF here. First, if L-PRF is mixed with the filling biomaterial (or even used as sole filling biomaterial), the immune and antibacterial properties [79, 123] of the L-PRF are highly beneficial when the avulsion sockets are damaged, infected and inflammatory Figs. (**3** and **4**): a L-PRF clot is a blood clot and promotes therefore the draining and recovery of the site [130, 131] without risking contamination and necrosis (contrarily to a bone biomaterial) ; the antibacterial and immune properties of the leukocyte-platelet gels were already pointed out in several applications and are currently a serious field of investigations [132-135]. Second, the surgical site can be covered with L-PRF membranes, in order to protect the bone compartment and to promote the induction of a thick and stable gingival tissue above the implant Figs. (**2** to **4**). This technique is then a variation of the NBR concept and this is of particular interest during immediate post-avulsion implantation, when the hollow cavity created after dental avulsion is difficult to cover with a gingival flap and to close with tight sutures: the L-PRF layers then protect the implant site from the agressive oral environment and accelerate the closure of the gingival gap. Moreover, the gingival tissues around damaged teeth are often compromised and present serious risks of necrosis and retraction after surgery; the use of the L-PRF layer allows also to stimulate these soft tissues and to promote their quick healing, necessary for an adequate covering of the implantation site Figs. (**3** and **4**). Finally, in some cases the peri-implant spaces can be very large (for example during immediate implantation after the avulsion of a large molar) and then the NBR principles should be fully used for the regeneration of the bone defect and the gingival hole (the 2 main compartments). The NBR technique can then be extended to the reshaping of a whole alveolar ridge, in order to obtain the best anatomical configuration for an ideal functional and esthetic implant-supported rehabilitation. This concept of alveolar ridges extensive reshaping is the latest evolution of the NBR, and offers new therapeutic perspectives.

As a conclusion, NBR is an efficient therapeutic strategy for most kinds of peri-implant bone defects. A last argument should also be considered: L-PRF is an inexpensive and user-friendly technique that can be used easily in daily practice. It is more simple and efficient than the use of GBR membranes [136] and of any other kinds of surgical adjuvants (particularly PRPs). There are therefore only advantages and no inconvenient in using NBR for the treatment of peri-implant bone defects, and this technique will probably become the gold standard in the near future. The main remaining question is now to determine the best surgical protocols in order to obtain the best possible clinical outcomes and what are the best bone biomaterials to associate with L-PRF for an optimal bone regeneration. Some answers may be obtained in another key application for L-PRF: the sinus-lift procedure.

5. PRP AND PRF DURING SINUS-LIFT SURGERY: A GOLDEN APPLICATION

The sinus-lift surgery is an excellent model of bone healing. The concept of this procedure is to lift the sinus membrane (or Schneiderian membrane) after lateral osteotomy in order to create an artificial subantral cavity. This cavity is generally filled with a bone biomaterial, and after a few months of healing and remodelling, dental implants can be inserted in the grafted bone volume. Sinus-lift bone grafting is considered to be a very secure procedure, and the consensus is that most bone materials (autologous, allogeneic, xenogeneic or synthetic) can give good results in terms of bone healing and implant survival (after implant placement in the grafted bone volume)[8, 137-139]. Indeed, the subsinus cavity is a natural bone regenerative chamber, covered by the Schneiderian membrane with high osteogeneic periosteum-like properties [140] and anatomically protected from the oral biomechanical constraints or parasitic forces. Most researches on the bone biomaterials for sinus-lift tried therefore to improve the quality of the regenerated bone volume and to accelerate its healing for early implant placement [141].

Another approach is to place the implants during the sinus-lift procedure in order to save time and avoid the second surgical procedure. In this method, the implants must be blocked in the residual alveolar bone height (for this reason, implants with microthreaded collars are often used for an easier mechanical blocking in the residual bone) and the tips of the implants maintain the sinus membrane in a high but natural position: therefore the implants are used as space maintainers like tent pegs. Then, the subantral cavity can be filled with a bone biomaterial [142-144] or only filled with a natural blood clot [72-74]. The filling with a blood clot only is enough to promote a limited but sufficient peri-implant bone volume [75, 145, 146]. This method illustrated that bone regeneration first requires to maintain and protect a bone regenerative chamber where the blood clot can promote the neoangiogenesis and the bone cell migration and proliferation. Most bone biomaterials used in sinus-lift have in fact this very same function of space maintainer for the blood clot. Therefore the addition of blood extracts like PRPs or optimized blood clot like L-PRF may be of significant interest [147].

Finally, the sinus-lift bone graft is a very efficient model for the evaluation of bone healing and remodelling in human clinical conditions. Indeed, a few months after grafting, when implants are placed in the bone graft, the first osteotomy can be performed with a trephine instead of a classical bone drill, and big human bone samples can be collected easily without raising any ethical issues: if not collected for analysis, these tissues would be anyway discarded during implantation. These bone cores are ideal samples for histological evaluation, and several bone cores can be collected per graft (since there are often more than 2 implants placed in a sinus bone graft). Sinus-lift is therefore one of the best *in vivo* human model for the testing of bone biomaterials in the maxillofacial area, and this explains why so many studies were performed on this model. However, if various PRPs were tested in many different configurations with various bone materials, the results were very contradictory.

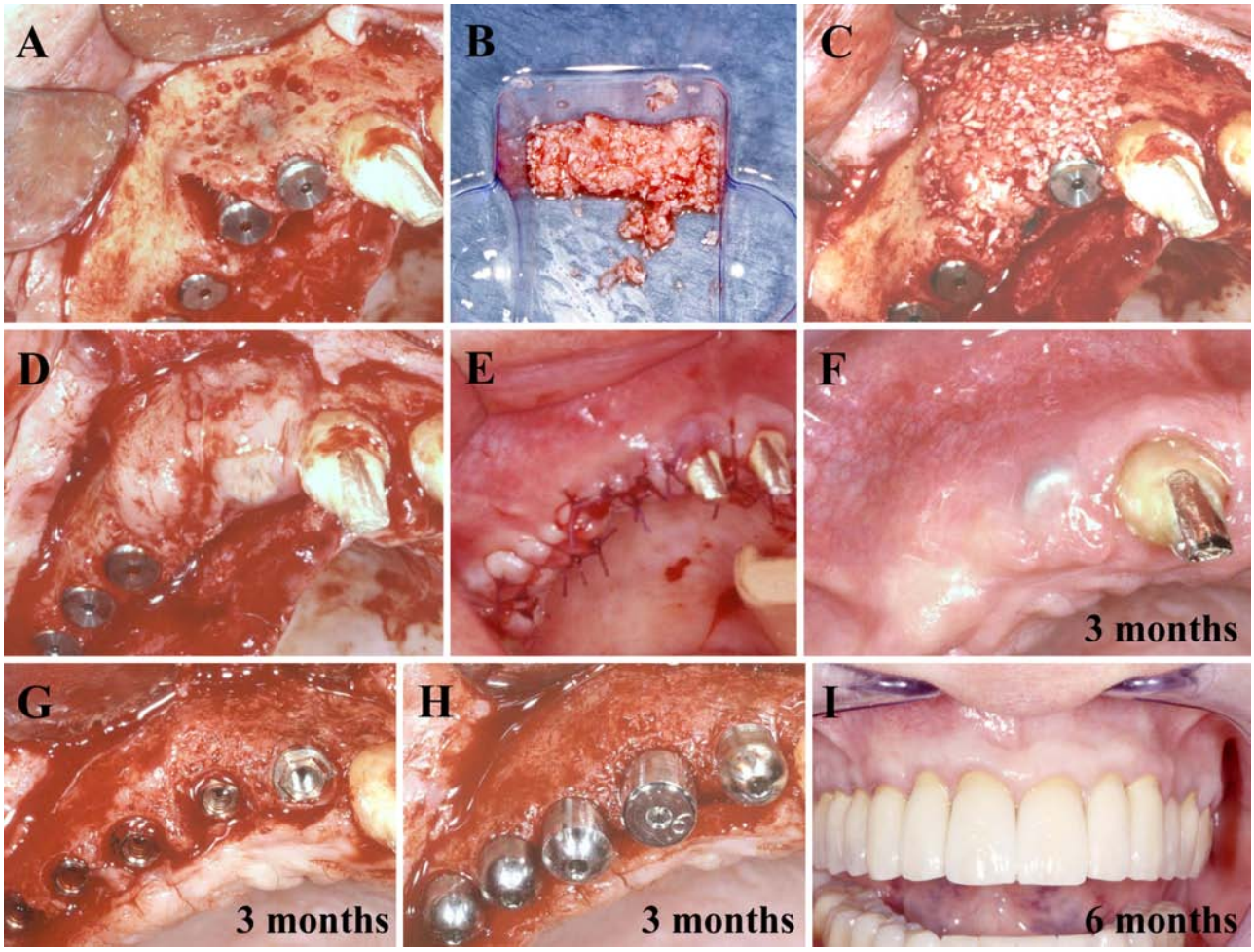

Fig. (2). Natural Bone Regeneration (NBR) with allograft of peri-implant bone defects created during immediate post-avulsion implantation. **A.** In this 65 years old patient treated in 2003, maxillary right lateral incisor and canine were damaged and infected. These teeth were therefore avulsed, the alveolar socket was carefully curetted and drilled for immediate post-avulsion implantation. The implants were blocked in the residual bone, but there were a large bone defect around the canine implant and a vestibular fenestration in front of the lateral incisor implant. The first step of the NBR procedure was to perforate the vestibular cortical bone with a small drill, in order to promote local bone bleeding (endosseous stimulation). Note that 3 other implants were also placed in the posterior right edentulous ridge. **B.** A bone grafting material was prepared using a mix of L-PRF and freeze-dried bone allograft (Phoenix allograft, TBF, Mions, France) in a 50/50 volumic ratio, in association with a 0.5% metronidazole solution. **C.** The grafting material was used to fill the peri-implant defects and also to cover and thicken the fenestrated vestibular bone ridge. The canine convex contour was recreated with the material. **D.** L-PRF membranes were covering the grafted area, stabilizing the grafting material and protecting the bone regeneration compartment. **E.** Tight sutures were performed. The gingival flap had to be pulled up the implanted and grafted alveolar sockets, since the covering tissue after the avulsions was too short. **F.** Three months after surgery, the gingival tissue was healed and thick, particularly above the former avulsion sockets. However, one cover screw was observable through ; the gingival tissue was quite thin in this area, probably because the implant head was too prominent after implantation, leading to mechanical constraints on the healing gingiva. **G** and **H.** Three months after implantation, the cover screws were removed and the transgingival healing screws could be connected. We observed that the peri-implant bone defects were completely regenerated and the vestibular side of the alveolar ridge was thickened. The grafted volume could not be distinguished from the original alveolar bone. **I.** Six months after implantation, the final prosthetic rehabilitation was performed. The final result was both very esthetic and functional, particularly in this complex case where bone volumes and soft tissues were compromised. Seven years after the treatment, the clinical result is still stable with no notable evolution of the bone levels or gingival aspect.

5.1. PRP During Sinus-Lift: Contradictory Results

Many studies reported that the addition of PRP to a sinus bone graft in many different configurations (with xenograft, βTCP, allograft, etc.) was associated with positive clinical outcomes, or at least did not show a negative impact on bone healing [148-158]. However the justifications for the use of PRP in sinus-lift were often quite empirical: a PRP gel was a good method to handle a bone graft material during the insertion in the subsinus cavity and could stimulate bone healing, but the level of proof remained quite weak since this surgical procedure presented already a quite high success rate without PRP.

On the contrary, when a more accurate evaluation of the true effects of PRPs during sinus-lift was performed, the

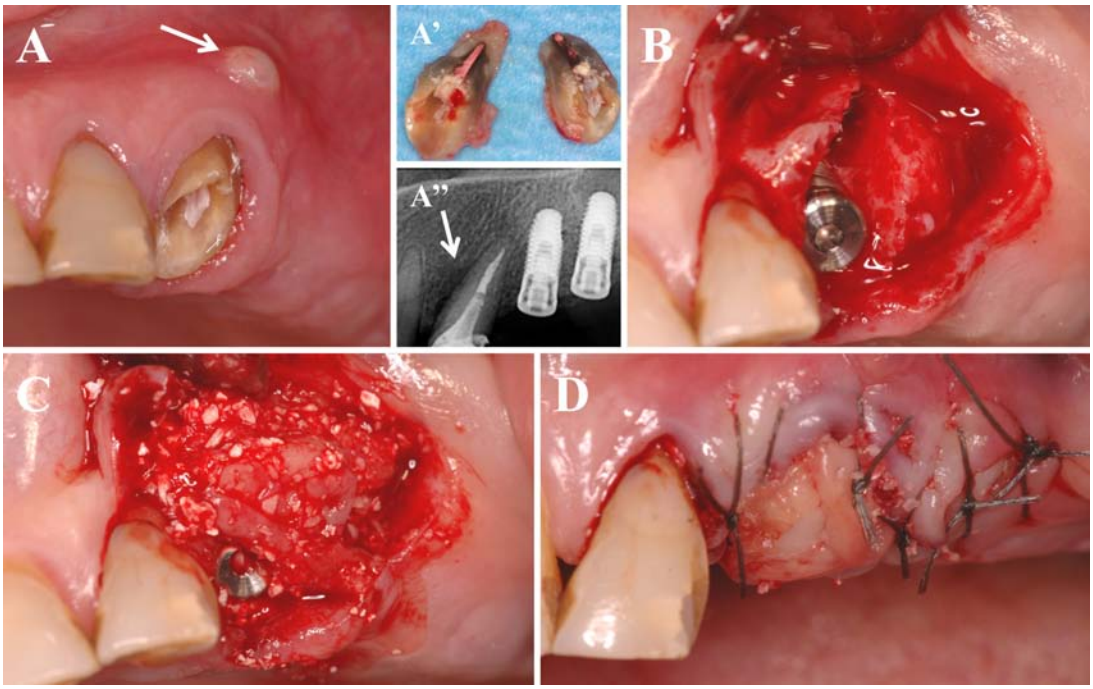

Fig. (3). Natural Bone Regeneration (NBR) with xenograft around peri-implant bone defects during immediate post-avulsion implantation in an infected avulsion socket. **A, A'** and **A''**. The left maxillary canine root was infected and associated with a large vestibular fistula (**A,** white arrow). The root was in fact broken, as observed after avulsion (**A'**). A deep periodontal lesion was observed on the radiograph (**A''**, white arrow), the periodontal bone was infected and compromised. **B.** The root was carefully avulsed, the avulsion socket was curetted and drilled for implant placement. The implant was blocked in the residual bone walls, but the peri-implant defect remained largely opened. **C.** The peri-implant defect was filled with a mix of L-PRF and xenogeneic collagenated bone (Gen-Os, OsteoBiol, Tecnoss, Italy) in a 50/50 volumic ratio, in association with a 0.5% metronidazole solution. The destroyed bone anatomy was restored with the bone grafting material. **D.** The grafted area was covered with a triple L-PRF layer in order to stabilize and protect the grafting volume from the oral environment. The gingival flap was damaged and too short after the avulsion for the complete covering of the implantation site, and tight sutures were not possible. The implantation site was therefore only covered and protected by the L-PRF layers, kept in direct contact with the oral environment.

reported data were most time quite negative. Many authors reported the absence of significant effects of various PRPs on the healing of a sinus bone graft done with autologous bone [159-163], allograft (DFDBA, FDBA)[164], xenograft (particularly anorganic bovine bone)[164-166], synthetic materials (bioactive glass for example)[162-164] or a combination of various materials [167]. Only very few authors reported a beneficial effect of PRP for bone healing after sinus-lift using FDBA [168], xenograft (anorganic bovine bone)[169], synthetic material (βTCP)[170] or autologous bone graft [171, 172], but it was suggested that this effect was limited to the early phases of healing only and did not influence the long term remodelling [170-172]. Finally, some other authors supported that the addition of PRP may not influence the final bone graft remodelling, but may increase the bone to implant contact of the implants placed in the grafted sinus [173]; unfortunately, most authors showed the contrary [162, 163, 165, 167].

It may seem impossible to draw extensive conclusions from these miscellaneous studies, because of the numerous methodological differences: the tested PRPs (and even the bone substitutes) were not accurately characterized, the surgical techniques and the way to combine PRP and bone materials were different between the various studies, and the bias related to the various *in vivo* models were numerous. However, the general conclusion of these heterogeneous studies is that if the PRPs present beneficial effects, they are scarce and difficult to point out. Even the few authors that noticed a potential positive effect of PRP on bone healing, also reported strictly no improvement in terms of clinical outcomes, particularly implant survival [169]. For these reasons, some authors recommended to avoid the use of PRPs during sinus-lift procedures [8, 174], since these expensive and time-consuming techniques did not lead clearly to an improvement of the bone quality or even of the surgical procedure, and therefore present no strategical therapeutic advantage.

If PRPs may not be useful in the daily practice of simple sinus-lift procedures, it does not mean that platelet concentrates may be completely useless. For example, the impact of L-PRPs on local infections, inflammatory reactions and for the regeneration of soft tissue dehiscences is also important [132, 133, 135, 175], particularly when there is a risk of tissue necrosis. Some authors showed that the use of PRP for the treatment of fistula following sinus-lift surgery was a very efficient option [176]. Unfortunately, these antibacterial and inflammatory regulatory aspects of some PRPs (particularly the L-PRPs) are often neglected in the literature.

Moreover, if the various PRPs tested in the literature did not give satisfactory results, it may be related to a misunder-

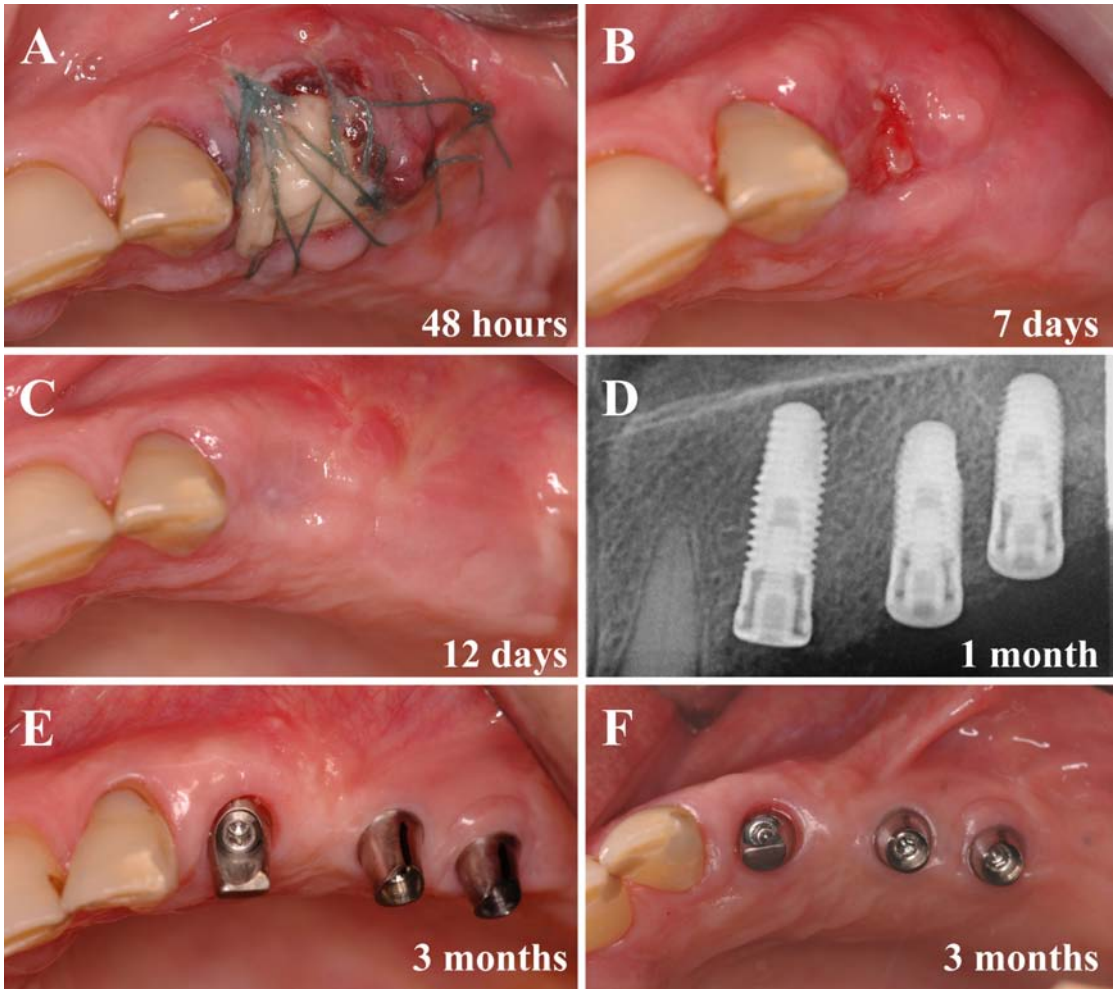

Fig. (4). Natural Bone Regeneration (NBR) with xenograft around peri-implant bone defects during immediate post-avulsion implantation in an infected avulsion socket. **A.** 48 hours after implantation, the strong superficial L-PRF membranes were still present and protecting the grafted area. The gingival tissue was in the induction phase and highly proliferative. **B.** Seven days after implantation, the gingival tissue was still proliferative, but the hole above the avulsion socket was filled with a reddish neo-tissue: the L-PRF matrix had supported the surface re-epithelialization and merged with the gingival flap into a regenerated connective tissue. **C.** Twelve days only after implantation, the surgical site was completely closed and already thick and strong. We were still in the remodelling phase. **D.** The radiographic follow-up after 1 month revealed an homogeneous bone quality around the implant, and no sign of the initial infection and defect. **E** and **F.** Two months after implantation, the transgingival healing screws were placed. One month later, the prosthetic abutments were connected to the implants. Three months after implantation, the alveolar ridge was perfectly healed and presented a large bone contour and a thick and stable peri-implant gingival tissue.

standing in the way to use them. PRPs were always used as surgical adjuvants for the promotion of an accelerated bone healing and eventually an improved implant anchorage. But maybe that their true potential is to be used in a different way, as tools for tissue engineering or *in situ* regenerative medicine. For example, when the PRP gel is used as cell carrier, the combination of bone mesenchymal stem cells (BMSC) and PRP with a bone substitute promoted better results (in terms of bone healing and osseointegration) than the bone material alone [177], and the use of BMSC loaded in a PRP gel as sinus filling material may be as efficient as autologous bone [178]. These tissue engineering options are not usable in daily clinical practice, but these results highlighted one of the main issues of the use of PRPs with bone biomaterials: how can a platelet concentrate rich in growth factors promote the induction of cell proliferation and differentiation when there are no cells or a limited quantity of cells? Moreover, cells need a strong fibrin architecture in order to migrate and proliferate within the bone chamber [179], and the PRP fibrin network is quite weak: it was reported that, when a fibrin glue is used to reinforce the fibrin architecture of a PRP, the combination of the platelet-enriched fibrin glue with an autologous bone graft promoted significantly better bone healing and enhanced implant osseointegration than the bone graft alone [180]. Finally, PRPs are blood extracts, and some authors reported that the use of various PRPs as sole filling material during sinus-lift procedure was promoting a strong bone regeneration [181], even equivalent to the graft of a bone substitute [182].

As a conclusion, what seemed to be missing to the PRPs for the promotion of a significant clinical improvement may be a strong fibrin architecture, the addition of living cells and

an adequate clinical methodology. For all these reasons, the use of L-PRF during sinus-lift may overcome all the limitations of the use of the PRPs in this application.

5.2. L-PRF During Sinus-Lift: a Golden Application

The quantity of publications about the use of L-PRF in sinus-lift is still limited, but the published data are homogeneous. The addition of L-PRF to a freeze-dried bone allograft (FDBA) allowed to obtain after 4 months the same histological bone healing and remodelling than FDBA alone after 8 months [76]: L-PRF accelerated the early healing of the sinus bone graft. The same methodology and FDBA/L-PRF combination were used in a series of 20 patients with bilateral sinus-lifts before implantation, and the implant survival rate was 100% after 5 years in these complex cases of global maxillary rehabilitation [77, 78]. Finally, the use of L-PRF as sole filling material in the subsinus cavity with simultaneous implant placement (Fig. **5**) promoted the large bone regeneration around the implants, as it was proven with histologic and radiologic analyses [70, 71, 183].

L-PRF may seem therefore to be more efficient, and less controversial, than PRPs. However, the true reasons of these reported successes are not only the intrinsic characteristics of the L-PRF, but also the clinical methodology associated with the L-PRF clots and membranes. Indeed, with its strong fibrin architecture [79], slow release of growth factors during more than 7 days [62, 63] and leukocyte content [60], L-PRF is no more a surgical adjuvant to a bone material: L-PRF is both a living tissue and a true solid biomaterial able to fill a significant volume in itself. The clinical methodology must therefore evolved and be adapted to the properties of the L-PRF clots and membranes.

The protocol to use with L-PRF in sinus-lift is in fact another variation of the powerful NBR concept, the main difference being that the subsinus cavity is a more protected bone regenerative chamber with a greater healing potential than the alveolar ridges. During sinus-lift, the actors of NBR are simply reversed, since the tissues to regenerate are inside and not superficial. First, the sinus membrane should be covered by several L-PRF membranes (Fig. **5**), in order to stimulate the bone regenerative periosteum-like properties of the Schneiderian membrane but also to patch all the visible or invisible tears in this membrane. The stimulation and protection of the sinus membrane is a key parameter for an improved healing and remodelling of the grafted volume, and the natural L-PRF membrane is probably one of the best material to use in this place: an optimized blood clot. Second, the filling material should be a combination of L-PRF with a bone substitute. L-PRF could be used alone when implants are inserted simultaneously and maintain the sinus membrane in high position (Fig. **5**), however the addition of a bone substitute is useful as space maintainer and osteoconductive matrix (Figs. **6** to **11**). Like in all NBR techniques, the choice of the best possible bone material to associate with L-PRF is now the main discussion and research subject. This bone grafting material should be soaked with a 0.5% metronidazole solution [129]. Finally, the lateral osteotomy window should be covered with a L-PRF layer, in order to stimulate the gingival periosteum and the regeneration of the bone window. Moreover, superficial layers of L-PRF can be added in order to improve the healing of the gingival flap and even the induction of a stronger gingival tissue.

This application of NBR principles to the sinus-lift is therefore not only a way to accelerate the bone healing, but it is in fact a larger concept to secure and improve the sinus grafting surgery. The use of L-PRF offers a protection and a better control of the healing of the sinus membrane, an acceleration of the bone graft remodelling, and an improvement of the gingival flap healing. Moreover, like other platelet-leukocyte gels [132, 135], L-PRF presents antibacterial and inflammatory regulatory properties that can be particularly useful when the sinus or the alveolar ridges above are damaged or not perfectly healthy (Figs. **6** to **11**). This NBR approach of the sinus-lift may be used only during complex or compromised sinus-lift procedures, but in our opinion and experience, this NBR approach should be used in all sinus-lift surgeries. It presents only technical and biological advantages, and no inconvenient. Contrarily to most PRP techniques, the L-PRF membranes are inexpensive and very easy to prepare. It is highly probable that the use of these L-PRF membranes will become a gold standard for secure and high-quality sinus grafting in the future. However, many studies are still necessary to validate the numerous potential clinical methodologies and combinations of L-PRF with other materials.

6. PRP AND PRF DURING IMPLANT GLOBAL REHABILITATION: BONE OR SOFT TISSUE REGENERATION?

Even if the experimental data about PRPs and bone healing remained quite contradictory, these techniques were often tested during implant global rehabilitations, where the addition of a healing booster may allow to increase the success rate of complex surgical procedures, such as split-crest bone expansion for implant placement [184], distraction osteogenesis for the restoration of severe atrophic mandible [185, 186], reconstruction of the severely resorbed maxilla with bone grafts [187-191] or preimplant onlay bone grafts [192, 193]. If some authors using PRPs were expecting an acceleration of bone healing, the main benefits of PRPs were probably to improve the soft tissue healing and therefore to reduce the risk of soft tissue dehiscences and perforations leading to the contamination of the surgical site and potential disastrous outcomes (such as infections and necrosis) ; the direct antibacterial and inflammation-regulatory properties of the PRPs could also be very useful to overcome such a local contamination [194]. Some authors reported also that the use of the PRP gel was interesting for an easier handling of the bone graft [187, 188]. However, in all these studies, the exact effects of the PRP gel were not demonstrated and their true impact on the clinical outcomes was difficult to point out [15]. It is interesting to note that most authors tried various PRPs without an accurate knowledge of the product they were using, and the PRPs were always used like a fibrin glue. PRPs are liquid/gel preparations and were therefore used as surgical adjuvants, and as it was discussed previously about sinus-lift, this may explain their limited beneficial impact. On the contrary, the L-PRF clots and membranes were not used as surgical adjuvants to the classical technique: they deeply modified the therapeutic approach of global implant-supported rehabilitations.

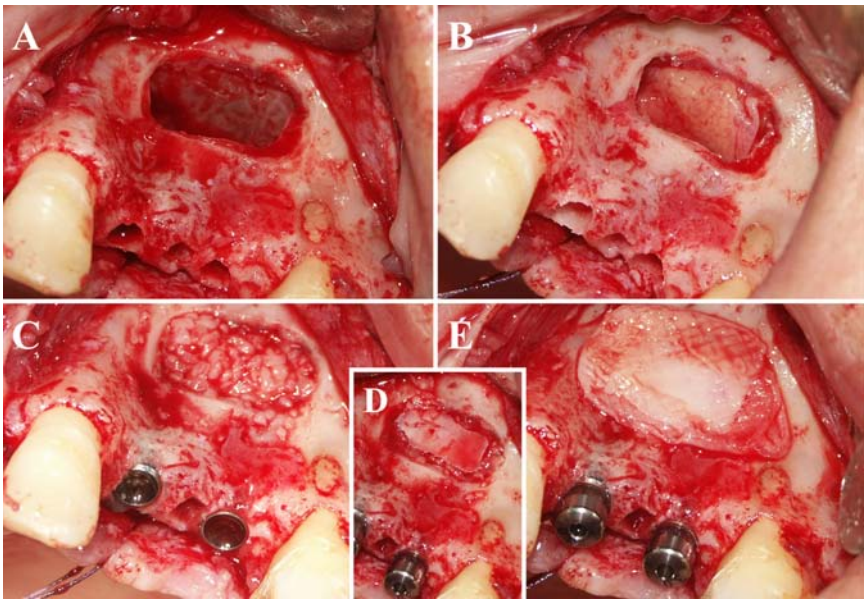

Fig. (5). Natural Bone Regeneration (NBR) during a sinus-lift procedure with simultaneous implant placement and L-PRF as sole filling material. **A.** After the lateral osteotomy, the Schneiderian membrane was lifted and therefore protected when the implant drillings were done. **B.** Two L-PRF membranes were placed to cover the Schneiderian membrane. C. Two Ossean Intra-Lock implants (Boca-Raton, Florida) were inserted and the implant tips were in contact with the L-PRF layer in order to maintain the Schneiderian membrane in high position. The subsinus cavity was then filled with L-PRF clots. **D** and **E.** The osteotomy window was closed with the original osteotomy bone fragment, and finally covered with a last L-PRF layer before sutures.

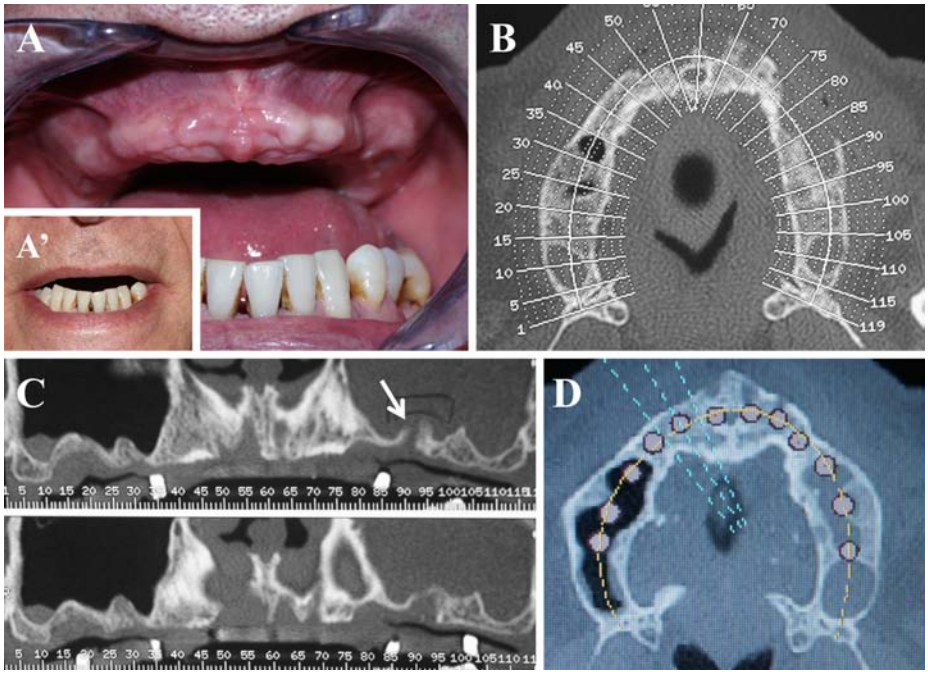

Fig. (6). Global implant-supported rehabilitation of the damaged maxillary using L-PRF, with bilateral sinus-lift and simultaneous implant placement. Initial situation. **A** and **A'**. This 57 years old patient presented a severe centripetal alveolar resorption with irregular alveolar ridges and gingival tissues, associated with the loss of the upper lip support. **B** and **C**. The X-ray tomodensitometric examination highlighted the major resorptions of the alveolar ridges, an uneven residual bone contour with many large bone defects (particularly on the left side), and a millimeter-thick subsinus residual bone height (SA4 sinus). In addition, the left sinus was filled with a large inflammatory mucous thickening, without clinical signs, seemingly caused by the infectious alveolar site around the left residual maxillary molar (white arrow). After avulsion a few months before, the tooth left behind a crater which resulted in a small oral-sinus communication. **D.** A surgical planification software was used on the X-ray scanner radiograph. The ideal positioning of the dental implants required to regenerate bone in the sinus and in several alveolar bone defects. This computed study was important for the validation of the therapeutic strategy in this resorbed and damaged maxilla. Using the L-PRF and the NBR principles, it was decided to achieve the complete implantation of the maxilla, with double sinus-lift and simultaneous implant placement in SA4 sinus.

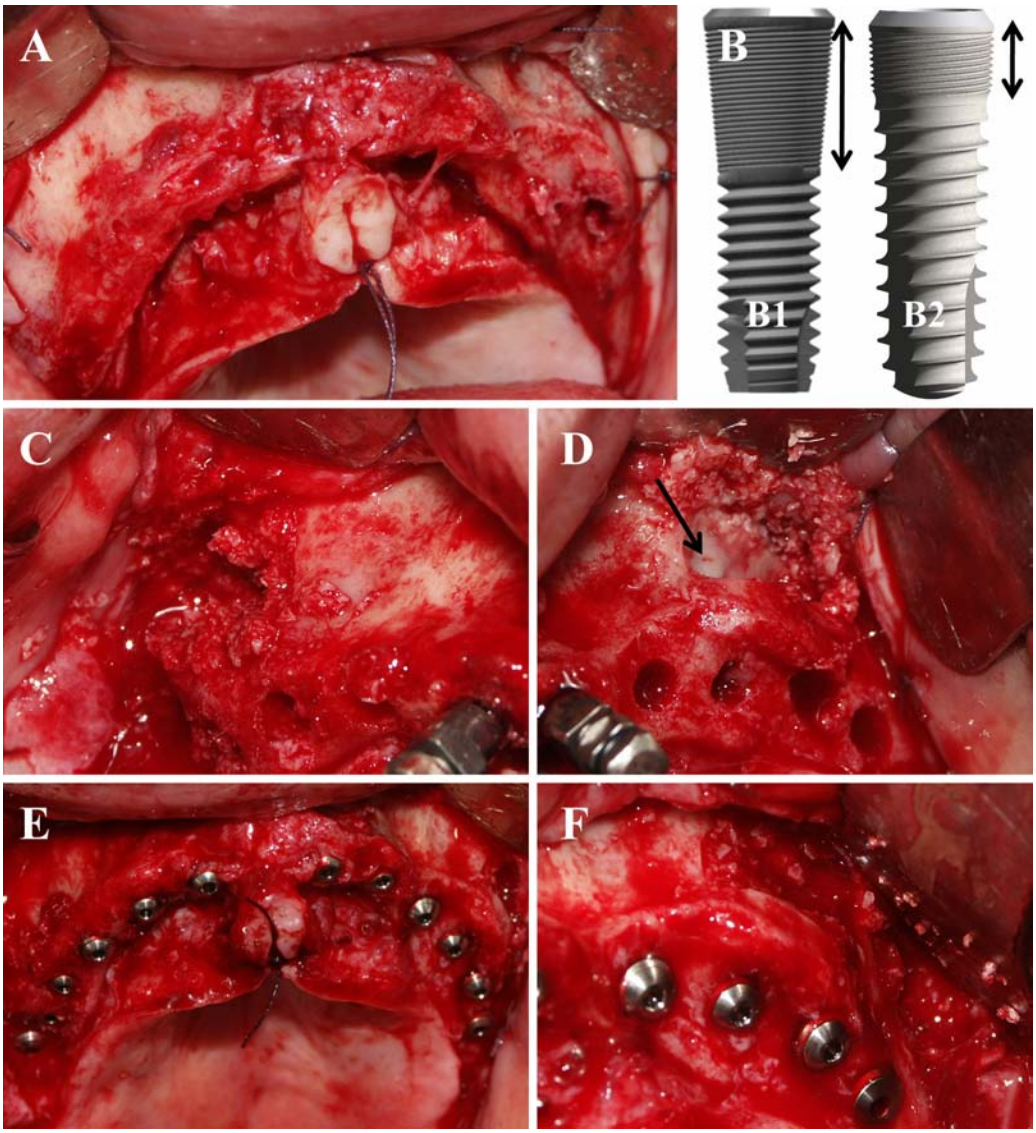

Fig. (7). Global implant-supported rehabilitation of the damaged maxillary using L-PRF, with bilateral sinus-lift and simultaneous implant placement. Surgical phase. **A.** The surgical site was largely opened, revealing the uneven bone contour and the perforation of the left posterior alveolar ridge (the oral-sinus communication). *B.* In complex rehabilitations, the use of improved implant design and surfaces is recommended, such as Osseospeed (B1, AstraTech, Mölndal, Sweden) or Ossean (B2, Intra-Lock, Boca-Raton, Florida, USA). These implants present a microthreaded collar (black arrows) that allows to block the implant in a millimeter-thick residual bone height and is therefore particularly useful in the subsinus area. **C** and **D**. After lateral osteotomy, the sinus membranes were lifted on both sides. The implant drilling was performed in the residual bone height, and the Schneiderian membranes were finally covered with a L-PRF layer (black arrow). The alveolar ridges were also corrected in order to keep a more regular contour. On the left side, the damaged alveolar area was curetted and finally the small oral-sinus communication was drilled in order to block an implant inside. **E** and **F**. The subsinus cavities were filled with a mix of L-PRF and freeze-dried bone allograft (Phoenix allograft, TBF, Mions, France) in a 50/50 volumic ratio, in association with a 0.5% metronidazole solution. Twelve AstraTech Osseospeed implants were then inserted and blocked in the residual alveolar ridges. On the left side, an implant was blocked successfully in the former oral-sinus communication. The same bone grafting combined material was used to fill the numerous bone defects of the alveolar ridges around the implants.

In the 2 parts of this article, we have described the numerous effects of L-PRF on bone and soft tissue healing and remodelling, and defined new therapeutical strategies associated to this biomaterial, particularly the Natural Tissue Regeneration (NTR) and Natural Bone Regeneration (NBR). The simultaneous use of all these therapeutical concepts offers new opportunities for the esthetic and functional implant-supported rehabilitation of severely resorbed or damaged maxilla [195]. As it is illustrated in the Figs. (**6** to **11**), a complex clinical situation in edentulous ridges often associates severe bone resorption and poor-quality gingival tissues, sometimes with sinus or bone infection and/or inflammation. The treatment strategy must be therefore both quantitative and qualitative: the reconstruction of adequate bone and gingival volumes and the regeneration of a natural and strong tissue architecture. The use of L-PRF during the sinus-lift

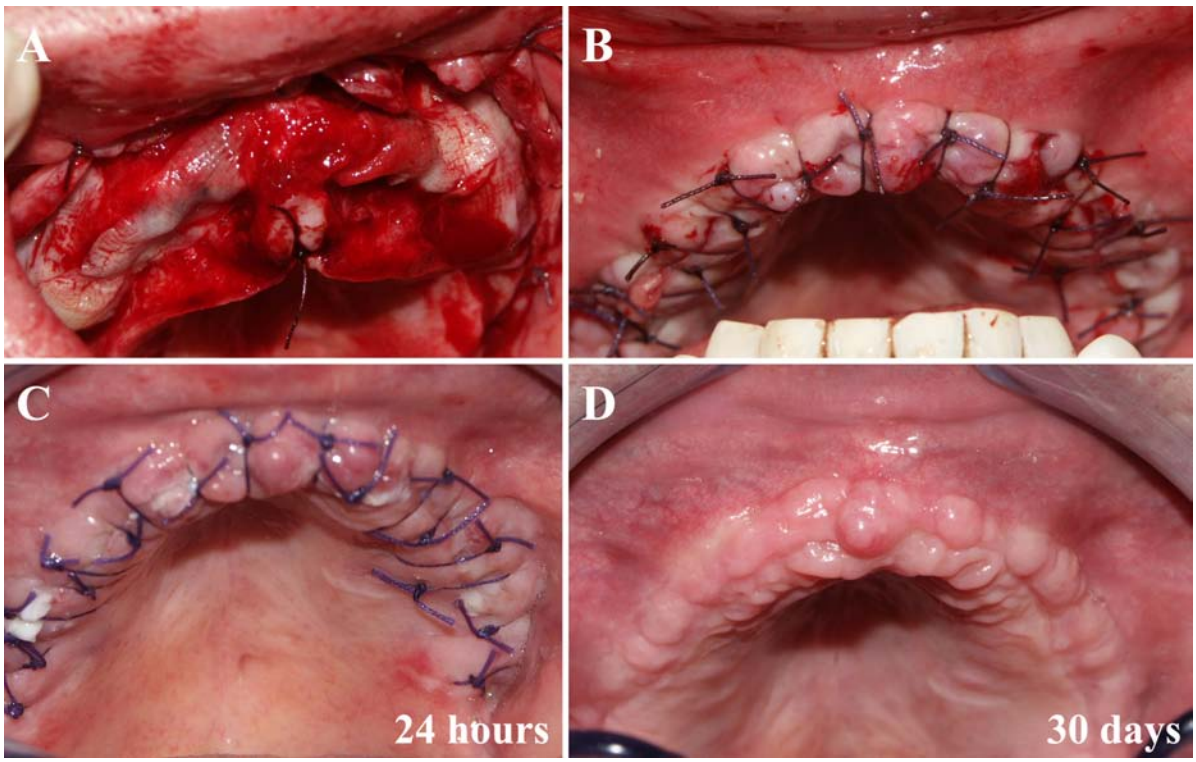

Fig. (8). Global implant-supported rehabilitation of the damaged maxillary using L-PRF, with bilateral sinus-lift and simultaneous implant placement. Early healing. **A.** The alveolar ridges were covered with L-PRF layers in order to protect the grafted material below and to improve the gingival healing and remodelling. **B.** The flaps were pulled up and tight sutures were performed in order to protect the grafted compartment, leading to a risk of insufficient vestibular keratinized gingiva. **C.** 24 hours after surgery, the incision line was almost closed, because of the healing stimulation promoted by the L-PRF layers. We were in the induction phase of the L-PRF-stimulated healing, and the gingiva seemed very proliferative. Post-operative pain and edema were also limited, as it was always reported when L-PRF layers are used to promote early neoangiogenesis on a wounded site. **D.** Thirty days after the surgery, gingival healing was complete and we were in the remodelling phase. However, the gingival surface was still uneven and proliferative. The thickening of the keratinized gingiva had been induced by the L-PRF layer and lasted several months.

allows to secure the bone graft in this compromised environment and to obtain a high quality bone volume Figs. (**6** and **9**). The use of the NBR principles for the treatment of peri-implant bone defects (or for the reconstruction of the alveolar ridges) allows to promote the regeneration of both bone and gingival compartments. Finally, the repetitive use of L-PRF layers under the gingival flap promotes the repetitive induction of a strong gingival healing and remodelling: a high quality gingiva is a key objective for an esthetic and biologically-stable clinical result Figs. (**8** and **11**).

The use of L-PRF promotes new therapeutic strategies, but the combination of this autologous material with other biotechnological tools can increase the quality and security of these complex treatments. For example, the use of high-quality implants with a microthreaded collar (in order to block firmly the implants in a thin residual bone height, particularly in the subsinus area), a platform switching prosthetic system (for a stable peri-implant bone level on a long-term basis)[196] and an improved implant surface can be of great help to promote the best possible clinical results and to extend the therapeutic potential [77, 78]. In our experience with complex clinical cases, we used this kind of implant design, with fluoride-modified surfaces (Osseospeed, AstraTech, Mölndal, Sweden)[85, 87] or nanorough and CaP low impregnated surfaces (Ossean, Intra-Lock, Boca-Raton, Florida, USA)[86, 197], and these high-quality implants offered more security and long-term stability than poorer implant design and surfaces [77, 78, 198]. Some other surgical adjuvants are also of great interest, such as the addition of a metronidazole solution to the bone grafting material in order to protect it from the unavoidable oral bacterial contaminations [129]. Finally, the choice of the best bone biomaterial to combine with the L-PRF during the NBR procedure remained a key issue: if we have a good experience with some specific freeze-dried bone allograft (FDBA)[76-78, 125, 126], other bone materials may promote even better results. The selection of the adequate bone substitutes (chemical composition, nano- and microscopic design, and macroscopic shape) in the various clinical situations and the best way to use them with L-PRF, is now one of the main research thematics in this field.

As a conclusion, even if some authors reported an interest in the addition of PRPs during complex implant treatments, they failed to define and validate accurately a true new and efficient therapeutic concept to associate with these products. The limited (and controversial) effects of PRPs on bone and soft tissue healing in these applications can not be a sufficient advantage to justify the use of these complex, ex-

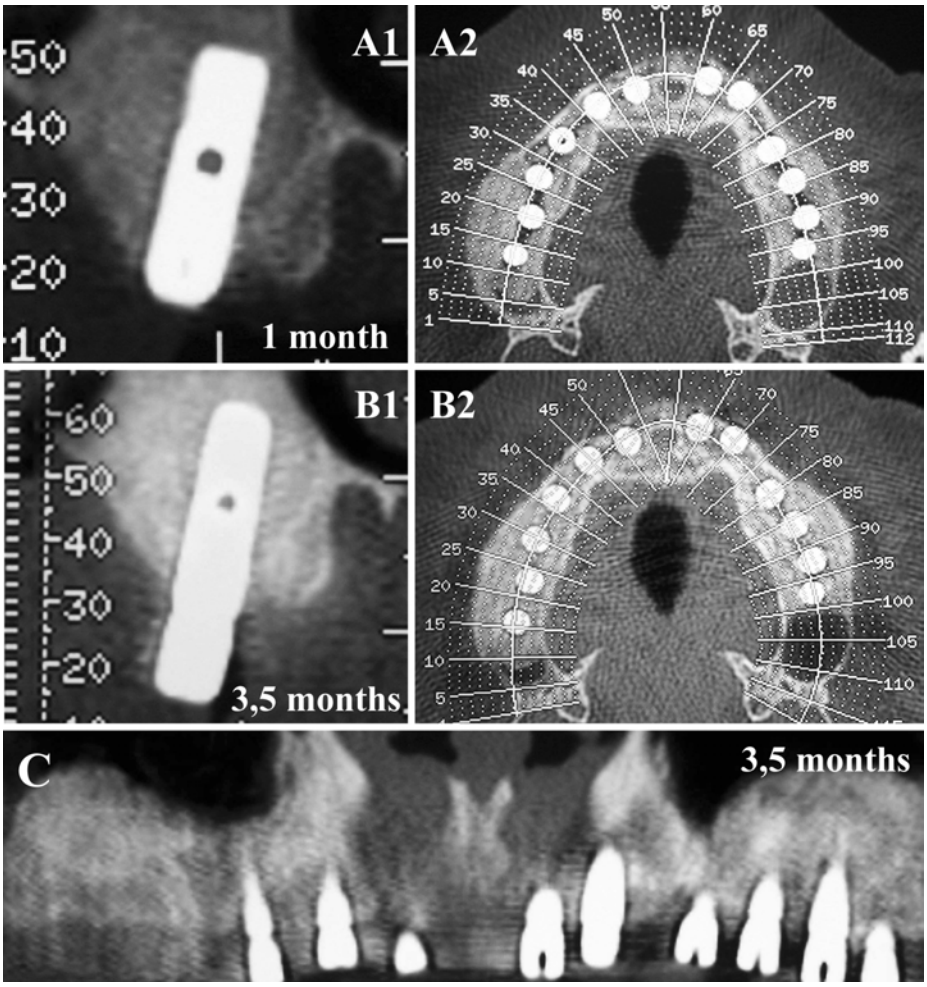

Fig. (9). Global implant-supported rehabilitation of the damaged maxillary using L-PRF, with bilateral sinus-lift and simultaneous implant placement. Radiographic follow-up. **A1** and *A2*. One month after surgery, a first X-ray tomodensitometric examination was performed. The large grafted area seemed homogeneous and stable (because of the metronidazole protection), but not very dense. **B1, B2** and **C**. The scanner taken 3.5 months post-operatively showed the high homogeneity and density of the grafted volume, particularly in the sinus-lift area. Moreover, the large intra-sinus mucous proliferative inflammation had completely disappeared, probably because of a synergy of factors (anti-infectious effect of metronidazole, and the stimulation of healing, neoangiogeneis and the associated drainage promoted by the L-PRF). The comparison of radiological bone densities on the scanners taken at 1 month and 3.5 months post-operatively illustrated the evolution of the density of the grafted volumes. The quality of the bone after 3.5 months suggested that the implants were ready for function and final prosthetic restoration.

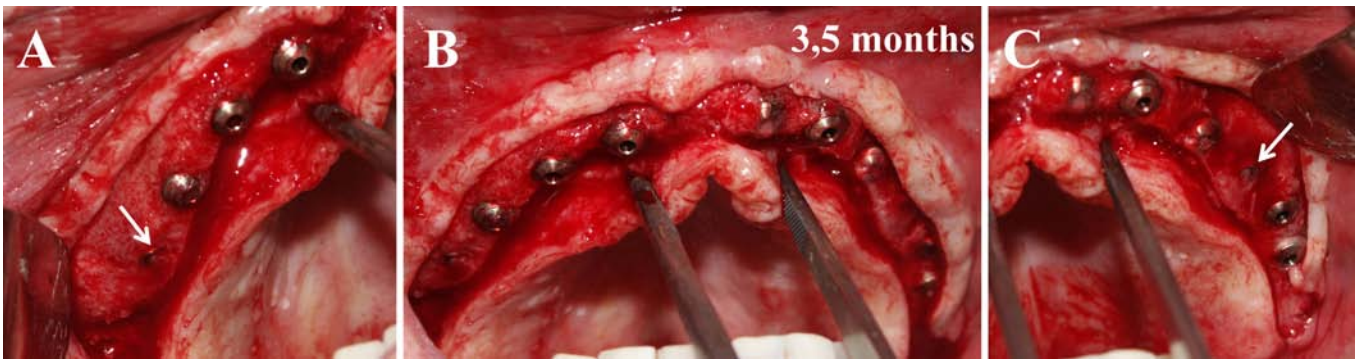

Fig. (10). Global implant-supported rehabilitation of the damaged maxillary using L-PRF, with bilateral sinus-lift and simultaneous implant placement. Reopening. Three and a half months (105 days) after implantation, the surgical site was reopened in order to remove the cover screws and to connect the transgingival healing screws. The grafted bone tissue displayed a dense and homogenous aspect and could not be distinguished from the original alveolar ridge. The L-PRF layers stimulated the periosteum and some implant heads were covered by new regenerated bone (white arrows) that had to be eliminated. The gingival flap was thick and homogeneous.

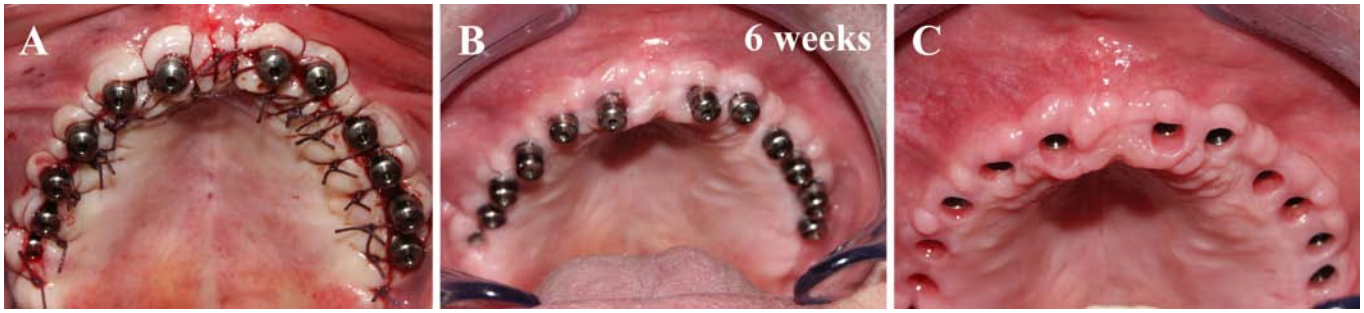

Fig. (11). Global implant-supported rehabilitation of the damaged maxillary using L-PRF, with bilateral sinus-lift and simultaneous implant placement. Final healing. **A.** In order to promote a repetitive induction on the gingival tissues, L-PRF layers were placed around the transgingival healing screws, and the gingival flaps were then sutured around the implant heads. **B.** 6 weeks after the second surgical phase, the gingival tissue was completely healed and very thick, but still displayed a proliferative aspect because of the second L-PRF induction. It was then possible to start the prosthetic phase. **C.** The healing screws were then removed for the preparation of the final implant-supported prosthesis. The thickness and quality of the peri-implant keratinized gingiva were considerable, and were the keys for a long-term esthetic and functional result. Finally, despite the initial significant maxillary bone resorption, the treatment lasted only less than 6 months. Five years after the treatment, the peri-implant bone levels and soft tissues are very stable. This successful strategy was driven by the use of L-PRF and associated biotechnologies.

pensive and time-consuming techniques. On the contrary, the combination of L-PRF and other applied biotechnologies allows to define new therapeutic concepts, to open a new range of therapeutic options for improved global esthetic and functional implant-supported rehabilitations and to push away some of the actual technical limits of these treatments [195]. These new therapeutic evolutions are one of the most exciting perspectives of the use of leukocyte-platelet concentrates in oral and maxillofacial surgery, and require an extensive research and development in the future.

7. PRP AND PRF: GENERAL APPLICATIONS IN ORAL AND MAXILLOFACIAL SURGERY

In oral and maxillofacial surgery, PRPs were very often tested during bone reconstruction for dental implant placement, however many other potential applications exist in this large field of surgery. Unfortunately, the literature about these general applications of PRPs remains quite scarce, even if some very interesting aspects were highlighted and discussed.

The article of Marx *et al.* that launched the « craze for growth factors », was a study about the addition of a PRP during large bone grafts in maxillofacial reconstructive surgery [5]. This application was tested in several clinical situations, particularly the treatement of alveolar cleft [199-201] and the reconstruction of bone defects after resection of large malignant tumours of the mandible, extended odontogenic cysts [202] or fibrous dysplasia [203]. Some authors claimed a beneficial impact of the PRPs in these maxillofacial reconstructive applications [5, 199, 202, 203], while other authors claimed the contrary [200, 201], but the level of proof remained anyway quite limited in these studies. As it was discussed previously, the true impact of PRP as surgical adjuvant for the stimulation of bone healing was difficult to point out and remained hotly debated.

However, some of the published data are of particular interests. When the maxillofacial tissues are compromised because of pharmaceutical or physical treatments, the use of platelet concentrates may be a great opportunity to reduce and control the risks associated to delayed bone and soft tissue healing. Three very frequent clinical situations started to be discussed and evaluated in the literature.

First, patients using bisphosphonates (particularly for the treatment of osteoporosis) present a reduced healing potential and a serious risk of delayed bone and soft tissue healing after oral and maxillofacial surgery that can lead to severe bisphosphonate-induced osteonecrosis. The addition of platelet growth factors on the surgical sites (for example during dental avulsions) in order to stimulate bone and soft tissue healing could be an interesting solution for the prevention of the bisphosphonate-induced osteonecrosis of the jaw [204]. Some other authors also reported the use of PRP for the treatment of the bone defects after the resection of the bisphosphonate-induced osteonecrosed tissues [205, 206]. The data about these techniques are limited (mainly case reports), but are of great interest considering the increasing number of patients treated with bisphosphonates. The use of a platelet concentrate could be considered as a preventive solution for these numerous patients, even if more complete studies are still necessary to validate this approach.

Second, patients using long-term anticoagulant therapies present a risk of delayed bleeding (and potential hemorrhage) and the associated delayed healing after oral and maxillofacial surgery. PRPs also concentrate coagulation factors and fibrin gel, and are therefore some kind of artificial blood clot [207]: their use as natural hemostatic local agent promoted good clinical results [208]. Moreover, healing is dependent on the initial blood clot after coagulation [130], and the addition of an artificial blood clot may therefore allow to stimulate the early healing phases in these patients. However, the beneficial impact of PRPs has still to be validated carefully in the various potential applications in anticoagulated patients.

Third, the post-tumoral reconstruction of a bone defect in the irradiated mandible or maxillary in cancer patients is also a challenge, since the irradiation destroyed most of the heal-

ing potential of the tissues locally. Therefore, the addition of PRPs may be of great interest in order to stimulate locally the healing potential and to avoid a post-surgical osteonecrosis of the jaw [209]. Even if the first experiences were positive, the literature on this topic remained very experimental and limited [210], and more research is necessary to validate this approach.

These data suggest that, even if PRPs way not be very useful when the lesions are limited in a healthy patient, their use may be more beneficial when the general health conditions of the tissues are compromised. However, the range of possibilities is very large in maxillofacial surgery and medicine, and many other potential applications can be suggested, such as the use of PRP as fibrin glue and healing stimulator on nerves (particularly for the facial nerve regeneration)[211-214], adipocytes [215] and other tissues. The exact impact of PRPs on the peripheric tissues after the resection of a cancer lesion should also be examined carefully. Unfortunately, these potential fields of research are quite neglected, probably because most PRPs failed to show a clear beneficial therapeutic impact in other fields of maxillofacial surgery, particularly during the healing of bone graft and other applications in periodontology and implant dentistry.

The literature about L-PRF in general maxillofacial surgery is even more scarce than the literature about PRP in these applications, because the L-PRF is a recent second-generation platelet concentrate technology [6, 122, 123] and quite far from the initial PRP production concepts. However, we have already a strong experience with L-PRF clots and membranes for the treatment of anticoagulated patients, and for the prevention and the treatment of the bisphosphonate-induced osteonecrosis of the jaw. Our preliminary results were very positive, but still require an extensive validation. Moreover, many other applications were also suggested in maxillofacial and ENT (Ear-Nose-Throat) surgery: contrarily to PRPs, L-PRF is a solid biomaterial with a quite significant volume that allows to fill cavities after tumoral exeresis (for example after parotidectomy)[216], alone or in association with grafted tissues (for example an adipocyte graft in facial reconstructive or plastic surgery)[217-219]. Our preliminary results were also satisfactory, and many new potential therapeutic opportunities should be investigated, particularly the impact of the L-PRF on the tissue regeneration after exeresis of tumoral malignant lesions. Moreover, L-PRF being an inexpensive and simple technique, there are only advantages to use it systematically in many different clinical situations. The careful development and validation of various surgical procedures using L-PRF represent an exciting perspective for the next years.

However, while developing new applications, it is important to keep in mind the intrinsic biology of these products in order to avoid misunderstandings. The relevance of L-PRF clots and membranes in oral and maxillofacial surgery is particularly strong because these materials have a form and a volume that strongly fit many surgical applications: this is true in periodontal surgery (as shown in the first part of this article), and promotes very good results in sinus-lift and implant dentistry. It does not mean that L-PRF will fit larger surgeries, where the membranes could not be handled and placed in the adequate conditions to promote tissue regeneration. As shown in the various examples described in these 2 articles, several oral and maxillofacial surgery procedures already used membranes (particularly during Guided Tissue Regeneration (GTR), GBR and sinus-lift) and tissue manipulation, and therefore L-PRF membranes intrinsically fit these applications: the use of L-PRF membranes was only a natural evolution of the concept. In other maxillofacial applications such as orthognathic surgery (Obwegeser or Lefort osteotomies for example), the use of L-PRF is less obvious and natural, and therefore requires first to define an adequate surgical methodology in order to benefit from the properties of the L-PRF and maybe to improve the clinical outcomes.

Finally, the potential applications of PRP and PRF in general oral and maxillofacial surgery and medicine are numerous and still neglected, particularly in patients with a damaged healing potential, and this specific field strongly requires further research.

CONCLUSIONS

The literature on platelet concentrates for topical use in oral and maxillofacial surgery is nowadays prolific and particularly developed in periodontology and implant dentistry, large fields of research remaining still unexplored in the maxillofacial area. Unfortunately, the published data are often contradictory and incomplete, particularly because of the lack of proper terminology and of extensive characterization of the tested platelet concentrates. Most published studies were done with P-PRP or L-PRP, and from the mass of the literature about these PRPs, it is difficult to claim a true relevance in their use in most clinical situations in oral and maxillofacial surgery. The situation is exactly the contrary with the L-PRF.

Like the living species, surgical techniques evolve and the most efficient protocols only survive. Injectable PRPs will probably develop more and more in many other fields of surgery over time, particularly sports medicine. However, if the craze for growth factors was very strong in oral and maxillofacial surgery, the disillusion was also very quick, many clinicians considering that the PRP techniques are too expensive and time-consuming for no or minimal clinical improvements. In the near future, simple, efficient and inexpensive techniques like the L-PRF will logically remain the major protocols used in oral and maxillofacial surgery.

Finally, it is also important to understand that whatever the product, these preparations rich in growth factors are not magical, and their successful use is completely dependent on the skills of the surgeons and their abilities to understand, prepare, use and combine correctly the technologies. PRP and PRF are at the borderline between the tissue engineering laboratory and the clinical practice, therefore their adequate use requires to have a biologically-driven vision of these products. This was true with PRP gels, and this is even more true with the L-PRF and the associated concepts of NTR and NBR. With these latter concepts, oral and maxillofacial surgery has entered in the era of regenerative medicine.

DISCLOSURE OF INTEREST

The authors declare no competing financial interests.

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