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REVIEW ARTICLE

APCs in sinus floor augmentation

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Abstract

After tooth loss in the posterior area of the maxilla, sinus floor elevation is often required to compensate the vertical bone loss due to sinus pneumatization. This narrative review reports on the potential benefits of autologous platelet concentrates (APCs) during this procedure. As for transcrestal approach, APCs have been used as "sole" substitute/graft. However, because of the low number of clinical trials available with PRGF, and even none for PRP, no definitive conclusions can be made regarding their efficacy. The number of studies on the use of L-PRF were outnumbered indicating good feasibility for vertical bone gain, with a high implant survival rate and a low degree of complications. PRP and PRGF have not been studied as a "single/sole" substitute for a one-stage lateral window approach, probably because of the weak physical characteristics of the membranes. L-PRF alone appears to be a predictable grafting material for lateral maxillary sinus grafting and a reduced RBH should not be considered as a risk factor. Compared to a "standard" bone substitute L-PRF shows slightly less vertical bone gain (consider enough membrane application and use of bony window as new sinus floor roof over the implant apices), enhanced early resorption (first 6 months after application), but a similar stable bone gain afterward. For a two-stage lateral window approach, APCs "alone" cannot be recommended, due to their weak withstand to the sinus pneumatization forces. APCs combined with bone substitutes seem to accelerate bone formation, without any additional benefits on the long-term new bone gain. The use of L-PRF membranes for the treatment of perforations appears to be an effective treatment option, but further clinical studies are needed to confirm this. Even though the abovementioned statements are based on large numbers of studies, additional RCTs comparing APCs with different types of grafting procedures for sinus elevation are needed.

KEYWORDS
autogenous platelet concentrates, lateral window technique, membrane perforation, Schneiderian membrane, sinus floor augmentation, sinus grafting, sinus lift, transcrestal technique

1 | INTRODUCTION

During the development of maxillary bone, the sinus cavities are formed via a continuous physiological process called pneumatization which causes the maxillary sinuses to expand into the adjacent anatomical structures such as the alveolar process. The cause and extent of sinus pneumatization remain unclear, but the following reasons have been proposed: heredity, craniofacial configuration, bone density, growth hormones, and air pressure in the sinus. cavity.[1–3]

Several studies have investigated the amount of sinus pneumatization following tooth extraction, reporting conflicting results. The extent of pneumatization ranges considerably.[4–7] After tooth removal in the posterior maxilla, the vertical dimension of the alveolar bone will consequently reduce from two directions (coronally and apically), with the risk of hampering an optimal implant positioning.[8,9] This resorption often occurs within a short period after tooth extraction and, as such, a reconstruction and elevation of the maxillary sinus might be necessary when implants are needed.

Several systematic reviews have documented that a transalveolar or lateral window sinus floor augmentation with the use of a bone graft/substitute can predictably increase the vertical bone height. Different types of bone substitutes have been used for space provision after elevation of the Schneiderian membrane. While autologous bone graft may be considered as the gold standard because of its osteogenicity, osteoinductivity, and osteoconductivity,[10] it is not commonly used in sinus augmentation procedures because of graft resorption and donor site morbidity. Furthermore, the evidence indicates that the outcome of bone substitutes is comparable with that of autologous bone.[11]

The use of blood alone instead of a bone substitute during sinus floor elevation has been advocated in several studies offering favorable outcomes.[12–18] The main advantages for the use of blood only, as introduced by Lundgren et al.,[19] include a reduced rate of complications and lower costs, beside avoiding the risk of having remaining graft particles in the grafted site as well as in the sinus.[12–18] However, this procedure remains still controversial. In sites with a residual bone height (RBH) < 4 mm, Nedir and co-workers[15,17] showed more new bone formation when grafting materials were used instead of blood only. Moreover, critical for such approach is the presence of an intact Schneiderian membrane. As a matter of fact, a perforation of the membrane is a common complication in sinus grafting procedures, occurring in 10 to 60% of the cases.[20,21] This high range is likely dependent to the surgical technique applied, skills/experience of the operator and the less thickness of the membrane itself.

Bone substitutes, such as allografts, bovine xenografts, and synthetic alloplasts, have been successfully used as alternative to autogenous grafts for sinus elevation even though they have been associated with lower amount of vital bone formation and a graft resorption rate.[22,23] Moreover, they were found to delay bone regeneration process compared with autogenous bone or the blood clot alone.[24–26]

Autologous platelet concentrates (APCs) have been considered a valid alternative to bone substitutes, because of the release of growth factors and their antibacterial capacity.[27] Several studies have been performed with leukocyte- and platelet-rich fibrin (L-PRF) because of the physical characteristics of L-PRF membranes (much stronger than the plasma rich in growth factors (PRGF) or platelet-rich plasma (PRP) gels), as well as its 100% autogenous nature and the high amount of growth factors released over a longer period.[28,29] However, in case of a two-stage sinus floor elevation (e.g., when simultaneous implant placement is not possible because of insufficient residual bone and lack of primary implant stability), According to the authors experience the use of these membranes alone cannot be recommended because they cannot withstand the pneumatization forces within the sinus leading to an early collapse/shrinkage.

Therefore, when using APC membranes as "sole" substitute during sinus lifting, implants need to be placed simultaneously to act as "tent poles" by keeping up the elevated Schneiderian membrane. If this is not feasible, a bone substitute is required to preserve the augmented space. However, a combination with APCs could still be beneficial by possibly enhancing the bone healing/formation.

L-PRF or PRGF membranes also present the great advantage of facilitating the healing of the sinus membrane after perforation and can be applied as a barrier membrane to seal the access bony window to the sinus.

This narrative review aims to evaluate the benefits of applying APCs during different approaches for sinus floor elevation, making a distinction between first and second generation platelet concentrates, summarizing not only the amount of bone generation, but also considering patient-reported outcome measures (PROMs).

This review included papers published before March 2023. For the transcrestal and one-stage lateral window approach, only case series, controlled clinical trials or RCTs in which APCs were used as "sole" substitute (thus not in combination with bone substitutes, statins, or enamel matrix derivatives) on humans were considered.

Conversely, in order to evaluate the benefit of APCs in combination with a bone substitute, in case of a two-stage lateral window approach, only RCTs with histological data were selected. It was decided to only consider demineralized/deproteinized bovine bone mineral (DBBM) as bone substitute to reduce the heterogeneity and because this material has been used in the majority of studies.

All clinical trials in this review applying PRF used a centrifugation protocol leading to high concentrations of leukocytes besides the platelet. Since a clear clinical difference between different modifications of PRF (including CGF, A-PRF, A-PRF$^+$ T-PRF, H-PRF) has not been reported so far, we group them all under the term L-PRF.

2 | TRANSCRESTAL APPROACH WITH PLATELET CONCENTRATES

The transcrestal approach is a well-established and effective technique for sinus augmentation based on creating an access to the sinus membrane through the implant site, followed by the detachment and cranially displacement of the sinus membrane. It was firstly documented by Tatum[9] and then modified by Summers,[30] who introduced a series of osteotomes. Compared with the lateral window approach, it results in a significantly reduced postoperative discomfort and swelling and is overall considered as less invasive.[31–33] However, it is widely accepted that a minimal residual bone height between 4 and 8 mm should be present for a predictable transcrestal sinus lift.[34–36] Since its introduction, different surgical techniques have been proposed. In particular, the access to the sinus can be created with rotating instruments, piezoelectric instruments, or a combination of osteotomes and trephine burs (for review see[37]). The use of a bone substitute in this procedure remains a matter of debate due to contrasting evidence on its benefit.[37–39]

APCs have been tested in several clinical trials dealing with the transcrestal approach. The rationale for their use relates mainly to space provision and to the possibility to accelerate the healing process. Moreover, APC membranes can provide protection to the sinus membrane while using an osteotome (cushion-like function), and, in case of sinus membrane perforation, they can facilitate its closure.[40]

The outcome of APCs when applied as "sole" substitute during a transcrestal sinus floor elevation are summarized in Table 1 (especially looking for vertical bone gain (VBG), implant survival and patient-related outcome variables (PROMs)).

2.1 | Platelet-rich plasma (PRP)

To the best of our knowledge, no studies have employed PRP during transcrestal sinus lift.

2.2 | Plasma rich in growth factors (PRGF)

One prospective study used PRGF as "sole" graft material during transcrestal sinus lift in combination with standard or short implants,[42] while another retrospective study used it alone or combined with a bone graft, in association with short implants[41] (Table 1).

2.2.1 | Bone gain and histology

Taschieri et al.[42] reported stable 5-year peri-implant radiographic bone levels when standard or short implants were employed in association with an osteotome sinus floor elevation and PRGF alone (mean change from 1 year of 0.05 ± 0.65 mm and 0.02 ± 0.80, respectively). Neither vertical bone gain nor histological data were provided.

In the retrospective study from Anitua and co-workers,[41] the mean radiographic bone gain at 5 months post-surgery employing PRGF alone was 4.64 ± 1.68 mm which was different from the mean gain obtained when PRGF was combined with an autologous graft or deproteinized bovine bone mineral (DBBM) or a mix of autologous graft and DBBM (4.88 ± 1.89 mm).

2.2.2 | Implant survival

The 5-year implant survival rate reported by Taschieri et al.[42] was 97.6% (97.7% for short implants and 97.4% for standard implants). The success rate, based on absence of mobility, pain, recurrent/persistent peri-implant infection, peri-implant radiolucency, and peri-implant bone loss ≥1 mm in the first year and ≥0.2 mm per year subsequently was 97.4% when using PRGF alone.

In the retrospective study employing PRGF alone or combined with a bone graft, an overall cumulative implant survival rate of 96.7% with a mean follow-up of 10.8 ± 5.8 months[41] was reported.

2.2.3 | PROMs

Anitua et al[41] indicated that out of 61 implants placed in 48 patients, perforation of the Schneiderian membrane occurred in one sinus which required a lateral wall access and the placement of a fibrin membrane to close the perforation. No surgical complications were reported in the other study.

2.3 | Leukocytes platelet-rich fibrin (L-PRF)

Several studies evaluated L-PRF as "sole" substitute for transcrestal sinus lift (Table 1). In particular, after discarding case reports, two RCTs,[48,50] seven prospective case series[40,43,45–47,49,52] and two retrospective studies[44,51] were evaluated. These studies were heterogeneous in terms of initial residual alveolar height (RBH), centrifugation protocol and number of L-PRF membranes/plugs applied during surgery. While simultaneous implant placement was always performed, the implant length and surface as well as healing protocol (submerged vs. unsubmerged) differed between the studies. All the above considerations made it challenging to compare the study outcomes and to draw robust conclusions.

2.3.1 | Bone gain and histology

Overall, the VBG after transcrestal sinus lift with L-PRF ranged from 2.6 mm to more than 10 mm, with most studies reporting a gain between 3.4 and 5.0 mm. (Figure 1).

One RCT compared a transcrestal approach using L-PRF alone with a lateral window approach employing DBBM and a collagen membrane.[50] This study indicated that the latter approach offered equal marginal bone loss, but more vertical bone gain with a higher bone density (even though this difference reduced over time). Another RCT compared a transcrestal sinus lift using either saline or L-PRF[48] and reported a significantly higher VBG when L-PRF was employed (2.6 ± 1.1 mm vs. 1.7 ± 1.0 mm). While the latter study showed the feasibility of hydraulic transcrestal sinus lifting without bone graft, it also clarified that adjunctive grafting (L-PRF, bone substitute) is advisable for cases requiring more than 2 mm intra-sinus bone gain.

TABLE 1 Characteristics of studies on the use of APCs alone in the transcrestal approach.

Article	Study type	Subjects: gender/age % smokers	Info on surgery RBH *(mm)* number of implants healing time	Centrifuge RPM or g force/ minutes	Treatment RCTs: *T* = test, *C* = control *(number of patients)*	Outcome: vertical bone gain (VBG) implant survival *PROMs*
PRP as sole substitute						
No papers available						
PRGF as sole substitute						
Anitua et al. 2015[41]	Retrospective case–control	♀ = 27/♂ = 21$^{\Sigma}$ Age: 56 ± 9$^{\Sigma}$ Smokers = 8%$^{\Sigma}$	RBH^{+G} = 4.4 ± 0.5 mm RBH^{-G} = 4.0 ± 0.5 mm 61 implants (+G: 27; −G: 34) 8 m	Endoret BTI PRGF 580 g/8 min	+G = 1: well-retracted fibrin plug + AB or AB and DBBM or DBBM −G = 1 well-retracted fibrin plug	- VBG^{+G} = 4.9 ± 1.9 mm at 5 m - VBG^{-G} = 4.6 ± 1.7 mm at 5 m Similar VBG with/without bone substitute Impl survival 96.7% up to 38 m$^{\Sigma}$ *1 membrane perforation*$^{\Sigma}$
Taschieri et al. 2018[42]	Case series	51 - -	RBH = 4–7 127 implants 5–6 m	Endoret BTI PRGF 580 g/8 min	1 well-retracted fibrin plug from F1	5 years impl survival = 97.7% for short and 97.4 for standard implants *7 prosthetic complications*
L-PRF as sole substitute						
Diss et al. 2008[40]	Case series	♀ = 14/♂ = 6 Age: 35–73 Smokers = 15%	RBH = 4–7 mm 35 implants 6–12 w	- 3.000 rpm/10 min	≥3 membranes	- VBG = 3.2 mm ± 1.5 1 year impl survival = 97.1% *7 membrane perforations* *2 sensations of blocked nose*
Toffler et al. 2010[43]	Case series	♀ = 70/♂ = 40 Age: 34–90 Smokers = -	RBH = 6.6 mm Range: 4–8 mm 138 implants 3 m	Process 2.700 rpm/12 min	2–4 membranes	- VBG = 3.4 mm (2.5–5 mm) - 1-11 m impl survival = 97.8% *5 membrane perforations* *2 nasal congestions*
Kim et al. 2014[44]	Case series (retrospective)	♀ = 5/♂ = 5 Age: 31–61 Smokers = -	RBH = 5.0 ± 2.8 mm 16 implants 24 w	Medifuge # settings	2–6 cloths	- VBG = 8.2 ± 2.9 mm at 6 m: - 8 m impl survival = 100% *No significant post-op complications*
Kanayama et al. 2016[45]	Case series	♀ = 15/♂ = 12 Age: 29–74 Smokers = -	RBH^{HA} = 2.7 ± 1.2 RBH^{SA} = 2.9 ± 1.1 39 implants 4–6 m	- 400 g/10 min	2 membranes	- VBG^{HA} = 4 mm at 1 year - VBG^{SA} = 4.4 mm at 1 year - 1 year impl survival = 100% *No significant post-op complications*
Testori et al. 2019[46]	Case series	♀ = 36/♂ = 17 Age: 29–72 Smokers = -	RBH = <4 mm 74 implants 6 months	IntraSpin 2.700 rpm/12 min	# plugs	- CSR = 93.3% at 5 years 3.1% peri-implantitis at 5 years *6 membrane perforations* *No symptoms of sinusitis*
Molemans et al. 2019[47]	Case series	♀ = 10/♂ = 12 Age: 38–78 Smokers = -	RBH = 5.8 ± 1.6 mm 22 implants 6 m	IntraSpin 2.700 rpm/12 min	≥3 L-PRF m	- VBG = 3.5 mm ± 1.4 at 6 m - 1 year impl survival = 91%
Cho et al. 2020[48]	RCT	♀ = 19/♂ = 21 Age: 27–70 Smokers = -	RBH = 6.8 ± 1.1 mm 40 implants 6 m	IntraSpin 2.700 rpm/12 min	T: # cloths (10) C: saline (10)	- VBG = T: 2.6 mm ± 1.1 at 1 year - VBG = C: 1.7 mm ± 1 at 1 year - 1 year impl survival = 100% *No significant post-op complications*

TABLE 1 (Continued)

Article	Study type	Subjects: gender/age % smokers	Info on surgery RBH *(mm)* number of implants healing time	Centrifuge RPM or g force/ minutes	Treatment RCTs: *T* = test, *C* = control *(number of patients)*	Outcome: vertical bone gain (VBG) implant survival *PROMs*
Wang et al. 2021[49]	Case series	♀ = 14/♂ = 6 Age: 27–73 Smokers = –	RBH = 2–5 mm 23 implants 4 m	- 3.000 rpm/10 min	# membranes	- VBG => 6 mm at 1 year - 1 year impl survival = 97% >bone mineral density with time *Low VAS pain score, no complications*
Lv et al. 2022[50]	RCT	♀ = 22/♂ = 28 Age: 44–54 Smokers = –	RBH ^{Tc} = 3.4 ± 0.8 mm RBH ^{LW} = 2.9 ± 0.6 mm 57 implants -	- 3.000 rpm/10 min	TC: 3 membranes/impl LW: DBBM + collagen m	TC: impl survival = 96.1% at 18 m LW: impl survival = 100% at 18 m >peri-implant bone height for LW *Significantly less post-op complications for TC*
Chen et al. 2022[51]	Retrospective case–control	♀ = 15/♂ = 29 Age: 21–73 Smokers = –	RBH^{+G} = 5.0 ± 0.6 mm RBH^{-G} = 5.2 ± 0.5 mm 60 implants 6 m	Medifuge # settings	+G = # membranes + DBBM (22) −G = # membranes alone (22)	- VBG at 6 m: +G: 5.1 vs. −G: 4.6 mm <early resorption in +G = 0.9 vs. −G 1.3 mm = resorption Year 1 & Year 2; 0.1 mm, respectively 2 years impl success = 100% >*pain in* +G group
Choudhary et al. 2022[52]	Case series	♀ = 8/♂ = 16 Age: 18–74 Smokers = –	RBH = 5.6 ± 0.7 mm 24 implants -	- 2.700 rpm/12 min	# clots cut in pieces	- VBG = 4.8 ± 2.2 at 6 m

Abbreviations: *Study type*: RCT = randomized clinical trial, retro = retrospective; 1 arm = study included several arms, but only 1 arm fulfilled required information ($^{\Sigma}$ data for all arms of study); *Info on surgery*: RBH = residual bone height; implants ^{HA} = hydroxyapatite implants, ^{SA} = sandblasted acid-etched implant; *Centrifuge data*: g = g-force; RPM = revolutions/rotations per minute; *Treatment*: # = several, +G = with bone graft, −G = without bone graft, LW = lateral window, TC = transcrestal; *Outcome*: AB = autologous bone, CSR = cumulative survival rate, impl = implant, PROMS in italic, VBG = vertical bone gain.

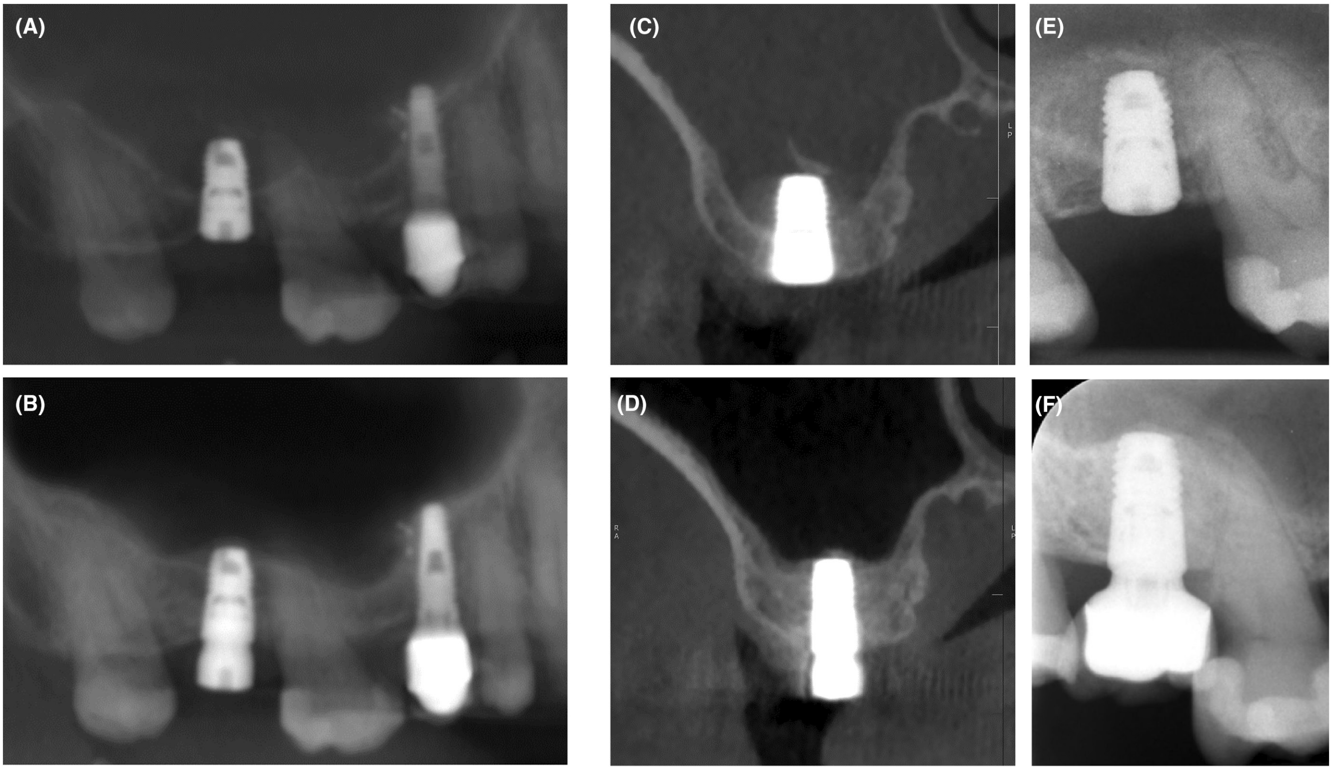


FIGURE 1 CBCT images (A, B): M-D; (C, D): B-P section, (A, C) immediately after transcrestal sinus floor elevation using L-PRF as sole substitute; (B, D) after 4 months of healing Intra-oral long-cone radiographs; (E): at the day of surgery; (F): 4 years later.

One recent retrospective observed an early reduction in the alveolar bone height during the first 6 months' post-transcrestal sinus lift (1.3 mm for L-PRF and 0.9 mm when combining with DBBM), which then stabilized in the following 2 years.[51]

This technique does not facilitate the harvesting of biopsies from the site, which would lead to confirmatory histological analysis of the quality of bone in the area. This limits the conclusions that can be made in relation to the use of L-PRF in this type of procedure.

2.3.2 | Implant survival

Most studies had a short follow-up and reported a 1-year implant survival rate ranging from 93.3% to 100%. Some trials with a longer follow-up presented a 2-year implant survival rate of 100%, or a 5-year cumulative survival rate of 93.3% when employing L-PRF for transcrestal sinus lift.

2.3.3 | Patient-reported outcome measures (PROMs)

A limited number of complications and adverse events have been reported when using L-PRF for transcrestal sinus lift, including sinus membrane perforation, physiologic post-surgery swelling, nose bleeding or sensation of blocked nose and headache. Interestingly, the initial RBH (<4 mm or ≥4 mm) is likely to play a role on the risk of complications[43] In the RCT comparing a transcrestal sinus lift with L-PRF to a lateral window approach employing deproteinized bovine bone mineral (DBBM) and a collagen membrane,[50] the incidence of intra-operative sinus perforations, as well as pain and swelling were significantly lower for the transcrestal approach.

2.4 | Conclusions

Because of the low number of clinical trials with PRGF and none for PRP no definitive conclusions can be made regarding their efficacy in transcrestal sinus floor elevation. The scientific evidence for the use of L-PRF for this indication is more robust indicating a feasibility for 3–4 mm vertical bone gain, with a high implant survival rate and a low degree of complications. Unfortunately, histological data on bone quality are lacking and RCTs with direct comparison to standard bone substitutes are sparse.

3 | ONE-STAGE LATERAL WINDOW APPROACH USING APCs AS "SOLE" GRAFTING MATERIAL

The lateral approach is the most documented surgical technique for maxillary sinus augmentation. Most of the literature is based on the use of autogenous bone[53,54] or bone substitutes.[55,56] However, many of the reported complications are due to granules loss through the sinus membrane perforations[57,58] inducing sinus infections.

It could be speculated that the use of APCs as "sole" grafting material might avoid or reduce the incidence of such complications, without jeopardizing the amount of VBG, and especially the implant survival rate overtime. The outcome of APCs when applied as "sole" substitute during a one-stage lateral window sinus floor elevation is summarized in Table 2. This approach is of course only indicated when the implants are placed simultaneously with the graft, to serve as "tent pool."

3.1 | Platelet-rich plasma (PRP)

To the best of our knowledge, no studies investigated the use of PRP for this purpose.

3.2 | Plasma rich in growth factors (PRGF)

To the best of our knowledge, no studies investigated the use of PRGF for this purpose.

3.3 | Leukocytes platelet-rich fibrin (L-PRF)

One RCT,[61] one CCT,[62] 4 prospective case series,[47,59,60,64] one retrospective case series[63] and one unpublished multicenter retrospective case series[65] explored L-PRF as "sole" grafting material (Table 2). These studies are slightly heterogeneous in terms of pre-op RBH (1.8–5.1 mm), centrifugation protocol, and number of L-PRF membranes/clots applied during surgery. However, the following strategies were often followed:

- 1–2 membranes were used to cover the Schneiderian membrane before the augmentation (to seal potentially present membrane tears);
- In case of sinus membrane perforation, they were successfully treated with L-PRF membranes;
- A large number of membranes are used to fill the open area after sinus floor lifting, before the insertion of the implant(s);
- Most authors suggested to keep the bony lid attached to the sinus membrane as a roof for the graft, except in two studies, where the bone window was completely removed by erosion using piezo-surgery,[62,65]
- L-PRF membranes are often used to seal the sinus access window,
- A healing period of 6 months before loading was mostly recommended, except in a recent study by Meyronin and coworkers, who choose a period of 4 months with the same results (Figure 2).[65]

3.3.1 | Bone gain and histology

Most authors reported a VBG of more than 4 mm (ranging from 3.4 to 10.4 mm). This bone gain seems directly dependent on the length of the implants and was often reported being in continuity with the implant apices. Simonpieri et al.[59] followed the bone gain over 6 years and did not observe clear changes over time.

The RBH at the day of sinus floor elevation did not seem to influence the outcome of the procedure, as confirmed by two studies,[59,62] treating patients with an average RBH of 1.8 mm[59] or a minimum of 1.0 mm,[62] respectively. Nevertheless, a reduced bone height could make it challenging to stabilize the implant, thus compromising implant stability.[59] In such situation, it would be advisable to undersize the drilling but, due to the reduced bone height the risk of crestal bone fracture increases. In order to prevent this risk by making this area more resistant, the coronal limit of the lateral bone window is moved apically 8–10 mm from the crest of the ridge. One solution would be to move the bone window 8–10 mm up to the crest of the ridge to provide a wide band of bone to prevent cracks and fracture.[66]

Biopsies from augmented areas with L-PRF as sole filling material showed the presence of "vital, well-vascularized" bone.[64] Moreover, the density of the generated bone, measured on CBCTs, was observed to be similar to the surrounding bone (Figures 2 and 3).[65]

One RCT[61] and one CCT[62] compared the outcome of L-PRF membranes with the use of a bone substitute and reported less VBG when using L-PRF alone (1.1 mm and 0.6 mm less, respectively), with similar graft resorption over time.

3.3.2 | Implant survival

Seven of the eight studies reported a 100% implant survival rate after a follow-up time ranging from 6 months to 6 years. Some studies applied the Albrektsson's[67] or Buser's criteria[68] for implant success and identified a very small number of unsuccessful implants (1 implant with bleeding on probing[61] and 1 nonintegration).[65]

3.3.3 | Patient-reported outcome measures (PROMs)

The studies, in which PROMs were evaluated, reported the absence of adverse events when applying L-PRF as single substitute. Sinus membrane perforations have been reported, but they were always successfully treated with L-PRF membranes.

3.4 | Conclusions

PRP and PRGF have not been studied as a "single" substitute for a one-stage lateral window approach, probably because of the weak physical characteristics of the membranes. L-PRF alone appears to be a predictable grafting material for lateral maxillary sinus grafting and a small RBH should not be considered as a risk factor. Compared with a "standard" bone substitute L-PRF shows slightly less vertical bone gain (consider enough membranes and use bony window as

TABLE 2 Characteristics of studies on the use of APCs alone in the lateral approach.

Author	Study type	Subjects: gender/ age % smokers	Info surgery: RBH *(mm) range* n implants impl loading	Centrifuge RPM/g force minutes	Treatment: substitute to fill sinus use of bony plate window substitute to seal window	Proms complications	Outcome: vertical bone gain (VBG) *range* implant survival rate histology
PRP or PRGF as sole substitute							
No papers available							
PRGF as sole substitute							
No papers available							
L-PRF as sole substitute							
Mazor et al. 2009 [(61)]	CS	♀ = 14/♂ = 6 Age: 41–65 Smokers: 10%	RBH = 2.9 ± 0.9 mm *(1.5–6 mm)* 41 implants 6 months	Process 400 g 12 min	2 L-PRF m + 4–5 cl *(compressed)* Bony plate = new sinus floor 1 L-PRF m over window	Uneventful healing Perforations treated with L-PRF m	6 m VBG = 10.4 ± 0.9 mm *(7–13 mm)* 6 m implant survival = 100% *33 ± 5% vital bone*
Simonpieri et al. 2011[59]	CS	♀ = 12/♂ = 8 Age: 37–80 Smokers: -	RBH = 1.8 ± 0.5 mm *(1–3 mm)* 52 implants ≥2–6 years	Process 400 g 12 min	2 L-PRF m + 4–5 cl *(compressed)* Bony plate: new floor/in window 1 L-PRF m over window	Uneventful healing 3 perforations treated with L-PRF m	VBG = 10.4 ± 1.2 mm *(8,5–12 mm) stable throughout the follow-up* ≥2–6 years implant survival = 100% NR
Tajima et al. 2013[60]	CS	♀ = 6/♂ = 0 Age: 53–82 Smokers: -	RBH = 4.3 ± 1 mm *(1.9–6.1 mm)* 17 implants 6 months	Medifuge MF200 # settings	2–4 L-PRF m Bony plate = new sinus floor 1 L-PRF m over window	NR NR	6 m VBG = 7.5 mm ± 1.5 Implant survival at ab connect = 100% *Mean bone density 323 ± 156 HU*
Molemans et al. 2019[47]	CS	♀ = 3/♂ = 3 Age: 41–68 Smokers: -	RBH = 4.4 ± 1.9 *NR* 7 implants 12 months	IntraSpin 2.700 rpm 12 min	4–6 L-PRF m Bony plate in window 1 m over window	NR NR	6 m VBG = 5.3 mm ± 1.7 1 year implant survival = 100% NR
Dominiak et al. 2021[61]	RCT *spl-m*	♀ = 16/♂ = 14 Age: 30–64 Smokers: -	RBH = 4–5 NR 15 implants 3 years	Process 3.000 rpm 10 min	C: Cerabone in sinus vs. T: # L-PRF m + cl in sinus Bony plate = new sinus floor 1 L-PRF m over window	No adverse effects T: 1 implant with peri-implant mucositis	3 years VBG: C = 4.5 vs. T = 3.4 mm, 3 years implant survival = 100% NR
Merli et al. 2022[62]	CCT *Non-R* *Parallel*	♀ = 10/♂ = 10 Age: mean 52 Smokers: 20%	RBH = 3 ± 0.8 *(1–4 mm)* 25 implants 6 months	Medifuge # settings	C: Bio-Oss in sinus & collagen m to cover window, T: 2–3 L-PRF m in sinus & 2 L-PRF m to cover window	No adverse effects Same patient Satisfaction	12 m VBG: C = 6.6 vs. T = 6 mm Similar graft resorption over first 12 m: C = 0.5 ± 1 vs. T = 0.7 ± 1.1 mm, 1 year implant survival = 100%

TABLE 2 (Continued)

Author	Study type	Subjects: gender/ age % smokers	Info surgery: RBH *(mm) range* n implants impl loading	Centrifuge RPM/g force minutes	Treatment: substitute to fill sinus use of bony plate window substitute to seal window	Proms complications	Outcome: vertical bone gain (VBG) *range* implant survival rate histology
Leighton et al. 2022[63]	Retro CS	♀ = 12/♂ = 8 Age: 49–78 Smokers: -	RBH = > 3 mm 21 implants 3 years	EBA 200 2.700 rpm 12 min	# L-PRF cl Bony plate = complete erosion 1 L-PRF m over window	No adverse effects 2 perforations treated with L-PRF m	5 m VBG = 63% of RBH 3 years implant survival = 100% NR
Meyronin et al. (submitted)	Retro CS	♀ = 18/♂ = 18 Age: 49–78 Smokers: -	RBH = 5.1 ± 1.6 *(1.5–9.5 mm)* 35 implants 2 years	IntraSpin 2.700 rpm 12 min	7 L-PRF m Bony plate = complete erosion 1 L-PRF m over window	No adverse effects 3 perforations treated with L-PRF m	4 m VBG = 4.6 ± 1.9 mm *(8.5–12 mm)* 2 years implant survival = 94.1% NR

Abbreviations: *Study type*: CCT = controlled clinical trial, CS = case series, non-R = nonrandomized, RCT = randomized clinical trial, retro = retrospective, spl-m = split-mouth; *Info on surgery*: RBH = residual bone height; *Centrifuge data*: g = g-force, rpm = revolutions/rotations per minute; *Treatment*: cl = clot, m = membrane; *Outcome*: ab connect = abutment connection, NR = not reported, VBG = vertical bone gain.

new sinus floor roof over the implant apices), earlier resorption (first 6 months after application), but a similar stable bone gain afterward.

4 | LATERAL WINDOW APPROACH USING APCs COMBINED WITH A BONE SUBSTITUTE AS GRAFTING MATERIAL

When it is not possible to place the implants simultaneously with the sinus floor augmentation (e.g., insufficient residual bone, insufficient implant stability), APC gels/membranes alone as filling material cannot be recommended because they cannot withstand the pneumatization forces within the sinus and will collapse/shrink within weeks, with limited bone formation.[69] Under these conditions one must add a bone substitute to better preserve the augmented space.

The question is whether APCs, when added to a bone substitute during two-stage sinus floor elevation, improve the healing (bone quality, implant integration, PROMs). Table 3 summarizes the benefits of adding APCs. Only studies including histology were considered. In order to increase the homogeneity between the studies we decided to only include RCTs where a DBBM was used as bone substitute.

4.1 | Platelet-rich plasma (PRP)

Only one RCT explored the adjunctive benefits of adding PRP to DBBM during a two-stage lateral window sinus elevation.[70] It failed to identify any significant benefits (Table 3). Recent systematic and narrative reviews explored the benefits when mixing PRP with other bone substitutes for two-stage sinus floor elevation[79,80] and they concluded, based on RCTs, that the histological, mechanical, and radiographic evaluations did not reveal an "obvious" adjunctive effect after the addition of PRP.

4.2 | Plasma rich in growth factors (PRGF)

Four RCTs with a split-mouth protocol[71–74] examined the benefits of adding PRGF to DBBM (Table 3).

4.2.1 | Histology

Three out of the four studies observed more new bone formation when PRGF was added, but only in one the difference reached statistical significance,[71] probably because of the low number of biopsies in the other papers. Two studies measured the amount of residual DBBM but failed to see any difference.

One study reported a statistically significant correlation between RBH and the amount of new bone formation.[73] However, this finding was not confirmed in other studies that have been using bone substitutes alone.[81,82]

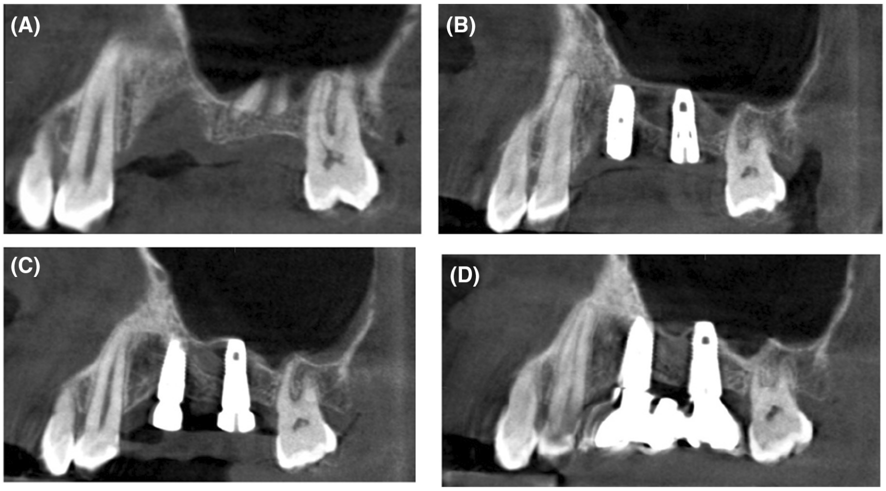


FIGURE 2 CBCT images of a 1-stage lateral window approach using L-PRF as sole substitute (A): pre-op situation, (B): immediate post-op, (C): 4 months' implant uncovering before loading, and (D): 2 years post loading; notice the increase in bone density over time.

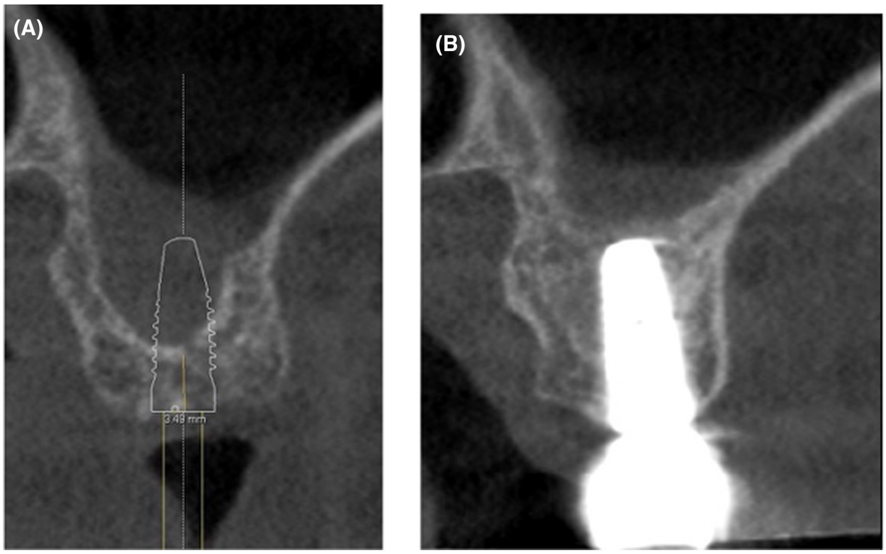


FIGURE 3 Detailed view of bone regeneration after one-stage lateral window approach using L-PRF as sole substitute. The bone density is similar for the pre-op native bone (A) and the regenerated bone 2 years post loading (B).

4.2.2 | Patient-reported outcome measures (PROMs)

All studies reported improved PROMs when PRGF had been added to the DBBM (less pain, and higher quality of life parameters post-surgery).[71–74]

4.3 | Leukocytes platelet-rich fibrin (L-PRF)

Four RCTs with a split-mouth design[75–78] explored the beneficial effect of adding L-PRF to DBBM (Table 3).

4.3.1 | Histology

In three of the four studies the addition of L-PRF resulted in more new bone formation and less residual bone substitute, but the differences were only statistically significant in one study.[77]

In the study by Pichotano et al.,[78] biopsies at the L-PRF + DBBM were taken after 4 months versus 8 months for the DBBM alone sites, and observed more new bone formation and less residual DBBM at the L-PRF sites. As a result, it was suggested by several authors that the healing time after sinus grafting before implant insertion can be reduced when a mixture L-PRF with a bone substitute is used.[78,83,84] However, contradictory data have been published by Nizam and co-workers and Adali et al., the latter using an allograft.[77,85]

The concomitant use of L-PRF, of course, also reduces the amount of bone substitute needed during surgery, and the amount of remaining bone graft particles in the healed graft. L-PRF indeed creates space that can easily be replaced by bone.[86]

4.3.2 | Patient-reported outcome measures (PROMs)

Ortega-Mejia et al.[86] and Gurler et al.[87] observed less complications when platelet concentrates had been used (less swelling, less pain).

TABLE 3 Characteristics of studies on the use of APCs associated with grafting in the lateral approach.

Article	Study design	Subjects: gender/age % smokers	Info surgery # sinuses, impl ins. RBH (mm)	Centrifuge procedure mL blood	Treatment *T* = test, *C* = control	Impact on parameters
A: PRP + DBBM as substitutes						
Cabbar et al. 2011[70]	RCT spl-m	♀ = 3/♂ = 7 Age: 53.7 ± 0.8 Smokers = −	20 sinuses, staged, ±5.2 mm	Curasan PRP Kit 10 mL	T (10): DBBM + PRP C (10): DBBM alone ⇒ 2 × 14 biopsies after 6,8 ± 0,9 m	***The addition of PRP gave***: = new bone (T: 16 vs. C: 16%) = residual graft (T: 24 vs. C: 22%) = soft-tissue (T: 58 vs. C: 60%)
B: PRGF + DBBM as substitutes						
Torres et al. 2009[71]	RCT spl-m	♀ = 3/♂ = 2 Age: 55–67 Smokers = −	5 sinuses, staged, 1–3 mm	BTI PRGF System II 10–20 mL	T (5): DBBM + PRGF C (5): DBBM alone ⇒ 2 × 5 biopsies after 6 m	***The addition of PRGF gave***: = augmentation on CBCT **>new bone (T: 31 vs. C: 21%)** = residual graft < connective tissue
Anitua et al. 2012[72]	RCT spl-m	♀ = 3/♂ = 2 Age: - Smokers = −	5 sinuses, staged, <1–3 mm	BTI PRGF System 70–90 mL	T (5): DBBM + PRGF C (5): DBBM alone ⇒ 2 × 2 biopsies after 6 m	***The addition of PRGF gave***: (only 2 cases with biopsies T & C): >new bone (T: 25 vs. C: 8%)
Taschieri et al. 2015[73]	RCT spl-m	♀ = 3/♂ = 2 Age: 48–71 Smokers = −	10 sinuses, Staged, <4 mm	BTI PRGF System IV - mL	T (5): DBBM + PRGF C (5): DBBM alone ⇒ 2 × 5 biopsies after 6 m	***The addition of PRGF gave***: >new bone (T: 31 vs. C: 23%)
Batas et al. 2019[74]	RCT spl-m	6 patients Age: - Smokers = −	12 sinuses, Staged, <3 mm	PRGF Vitoria System T	T (6): DBBM + PRGF C (6): DBBM alone ⇒ 2 × 6 biopsies after 6 m	***The addition of PRGF gave***: = new bone (T: 36 vs. C: 38%) = residual graft (T: 30 vs. C: 27%) = soft-tissue (T: 35 vs. C: 35%)
C: L-PRF + DBBM as substitutes						
Zhang et al. 2012[75]	RCT parallel	♀ = 2/♂ = 8 Age: 30–49 Smokers = −	11 sinuses, Staged, <5 mm	*Labofuge 300*: 300 g/10 min	T (6): DBBM + L-PRF cl ^{mix} + m ^{s} C (5): DBBM no m ⇒ 5 (C) + 6 (T) biopsies after 6 m	***The addition of L-PRF gave***: >new bone (T: 18 vs. C: 13%) < residual DBBM (T: 19 vs. C: 29%) >contact bone-substitute (T: 22 vs. C: 19%)
Bolukbasi et al. 2015[76]	RCT parallel	♀ = 15/♂ = 10 Mean age: 50.1 years Smokers = −	32 sinuses, staged, <5 mm	*Process* 400 g/12 min	T (17): DBBM + L-PRF cl$^{mix\ a}$ + m^{p,s} C (15): DBBM + CM^{p,s} ⇒ 15 (C) + 17 (T) biopsies after 6 m	***The addition of L-PRF gave***: = augmentation on CBCT >new bone (T: 35 vs. C: 33%) <residual DBBM (T: 33 vs. C: 34%)
Nizam et al. 2018[77]	RCT spl-m	♀ = 9/♂ = 4 Mean age: 49,9 years Smokers = −	26 sinuses, staged, <5 mm	*Nüve Laboratory* 400 g/12 min	T (13): DBBM + L-PRF cl$^{mix\ b}$ + CM^{s} C (13): DBBM Cm^{s} ⇒ 2 × 13 biopsies after 6 m	***The addition of L-PRF gave***: = bone volume (T: 21 vs. C: 21%) = residual DBBM (T: 26 vs. C: 33%)
Pichotano et al. 2019[78]	RCT spl-m	♀ = 6/♂ = 6 Mean age: 54,2 year Smokers = −	24 sinuses, staged, <4 mm	*Process* 300 g/10 min	T (12): DBBM + L-PRF m$^{mix\ c}$ + m^{p,s} C (12): DBBM alone no m ⇒ 2 × 12 biopsies after: **T = 4 m**/C = 8 m	***The addition of L-PRF gave***: **>new bone (T: 45 vs. C: 30%)** **<residual DBBM (T: 4 vs. C: 14%)**

Note: Data in bold = statistically significant.

Abbreviations: *Study type*: RCT = randomized clinical trial, spl-m = split-mouth; *info on surgery*: # = number of, RBH = residual bone height; *Centrifuge data*: *g* = g-force; *Treatment*: (..) is number of sinuses for each group respectively, *C* = control group, cl = clot, CM = collagen membrane, *m* = membrane, mix = mixture (a ratio clot/substitute 1:2, b ratio 3 clots on 1.5 g substitute, c ratio = 1 membrane on 0.5 g substitute), *p* = to protect Schneiderian membrane, *s* = to seal the window, *T* = test group.

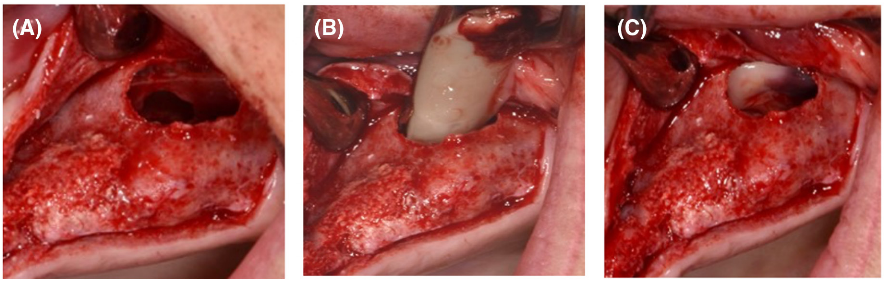


FIGURE 4 Closure of a sinus membrane perforation via a double layer of L-PRF membranes (face towards the perforation). The Schneiderian membrane moved again up and down when the patient was breathing.

4.4 | Conclusions

The addition of L-PRF to DBBM during a two-stage lateral window sinus lift showed only benefits in the early phase of healing (biopsies at 4 months), with only small adjunctive effects in biopsies taken at 6 months or later. It is suggested that L-PRF could accelerate new bone formation so that the implants could be inserted sooner, however, more studies with larger sample sizes are needed to confirm this hypothesis, based on the outcome of a single study.

5 | APC MEMBRANE TO CLOSE SINUS MEMBRANE TEAR/LATERAL ACCESS SINUS WINDOW

5.1 | Closure of membrane tear

The Schneiderian membrane, a respiratory mucosa, has under healthy conditions a limited thickness.[88] Monje and co-workers[89] reported, based on a meta-analysis of 19 studies, a mean thickness of 1.3 mm (95% CI = 1.1–1.6) when 3-D radiography was considered, and of 0.5 mm (95% CI 0.1–1.1) in case of histological examination. A perforation of this membrane during the preparation of the access bony window and/or during its detachment and elevation is one of the most frequent complications of an external sinus augmentation (occurring in 10% to 60% of the cases,[20,21,88] with most publications reporting rates between 20% and 25%).[90]

Schneiderian membrane tears come in different shapes and sizes, and their repair strategy depends on multiple factors including the size and location of the tear, the presence of pathology (tears created to remove cysts), the planning of simultaneous implant placement, and/or of the use of bone substitutes. The treatment strategy for a membrane tear depends on the extent of the perforation[90] For small perforations, especially when the membrane folds together, a special treatment might even not be needed since a simple reflection will obliterate the perforation. However, when closure is preferred, one can either seal the tear with a fibrin adhesive or a suture. For large perforations, covering the perforation with a resorbable collagen membrane extending over the bony margins (sometimes even fixed with tacks) is mostly applied. When such management fails or when the Schneiderian membrane is completely open, one should opt to abort the surgery and re-enter after a healing period of ≥6–8 weeks.[91,92] The question is whether APC gels/membranes could be used to seal medium to large membrane perforations (Figure 4).

5.1.1 | Platelet-rich plasma (PRP)

To the best of our knowledge, no studies investigated the use of PRP for this purpose.

5.1.2 | Plasma rich in growth factors (PRGF)

In one study,[93] PRGF gel membranes were employed to seal the sinus membrane perforation (1- or 2-stage approach, >10 mm in diameter), with at the 1-year follow-up a radiological normalization of the maxillary sinus in 17/18 patients, and an implant survival of 95% (35/37 implants).

5.1.3 | Leukocytes platelet-rich fibrin (L-PRF)

A pre-clinical study on rabbits[94] showed a similar histological healing of perforated sinus membranes (10 mm in diameter) treated either with a collagen membrane or with a L-PRF membrane. Xin et al.[95] compared, also in rabbits, the healing of perforated sinus membranes (3 mm in diameter) covered with an L-PRF or collagen membrane, with simultaneous bone grafting (two-stage approach). At 1 week, an intact sinus membrane was found in the L-PRF group. At 1- and 4-week post-op, the number of inflammatory cells at the perforated site was significantly higher in the collagen group, and the area of new osteoid formation was significantly greater in group L-PRF. There are two sources of osteogenesis in the elevated sinus floor area: osteogenesis from the basal bone, and osteogenesis from the sinus membrane.[96,97] In the collagen group, the osteogenesis originated solely from the basal bone, and the dense collagen structure caused untimely degradation, which hindered the repair of the sinus membrane. The L-PRF membrane in contrast established an intact micro-environment with low inflammation that was conducive to bone formation and remodeling.

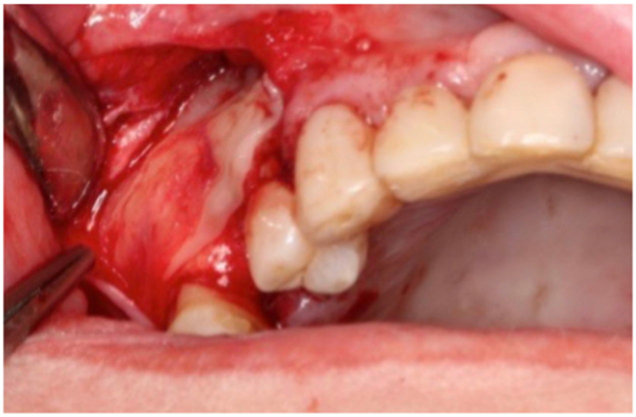


FIGURE 5 Coverage of the access window to the maxillary sinus with a double layer L-PRF membrane (face towards the window).

Two clinical case series confirmed the usefulness of this treatment strategy. After closure of a relatively large perforation with L-PRF membranes the augmentation procedure was continued in these studies[98–100] with a successful augmentation leading to a 100% survival rate of the implants, both for 1- or 2-stage approaches. The size of the included perforations was small to medium (<10 mm in diameter) for the study by Oncu and Kaymaz (2017), and large (>15 mm in diameter) in the study by de Almeida Malzoni and co-workers (2021).

Choukroun et al.[83] reported similar histomorphometric data (1 case) at 4 months' post sinus-lift in comparison to the "nonperforated membrane" cases.

5.2 | Closure of lateral window

The opening to the sinus after a lateral window approach is often sealed with a resorbable collagen membrane to reduce the proliferation of connective tissue into the sinus and to reduce the resorption of graft. Two RCTs compared several parameters including the rate of new bone formation and residual bone substitute for sinuses covered with either a collagen or a L-PRF membrane[101,102] (Figure 5). These studies reported similar outcomes for both types of membranes. Thus, one can conclude that an L-PRF membrane (probably a double layer) can be a viable and 100% autogenous alternative for covering a lateral window in the maxillary sinus.

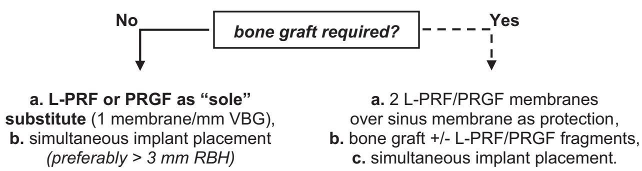
5.2.1 | Final conclusion

This paper searched for scientific evidence for the use of APCs as viable biomaterial in maxillary sinus augmentation. APCs (PRP, PRGF and L-PRF) offer a number of advantages including the high concentration of platelets and leukocytes (the latter not for PRGF), the release of growth factors crucial for wound healing (over a longer time in case of PRGF and especially L-PRF), an antibacterial capacity, anti-inflammatory effect, etc.

PRP and PRGF can only be prepared as fragile membranes, whereas L-PRF membranes, due to a resistant 3D fibrin network, have increased strength and can serve as barrier membranes (even to protect the Schneiderian membrane during implant placement and/or when applying a bone substitute).

5.2.2 | Transcrestal sinus floor elevation

A number of studies support the use of PRGF and especially of L-PRF as "sole" substitute. Most studies selected patients with a RBH of ≥3 mm. In general, one should expect a vertical bone gain of 3–4 mm. If more RBH gain is needed, one can opt for the use of a bone substitute, which can also be combined with an APC. Remarkably, also in the latter situation, L-PRF membranes might be useful to protect the Schneiderian membrane against the sharp bone substitute particles or implant apices (See decision tree, adapted from Miron and Pikos 2018). Moreover, L-PRF and PRGF seem to improve PROMs.

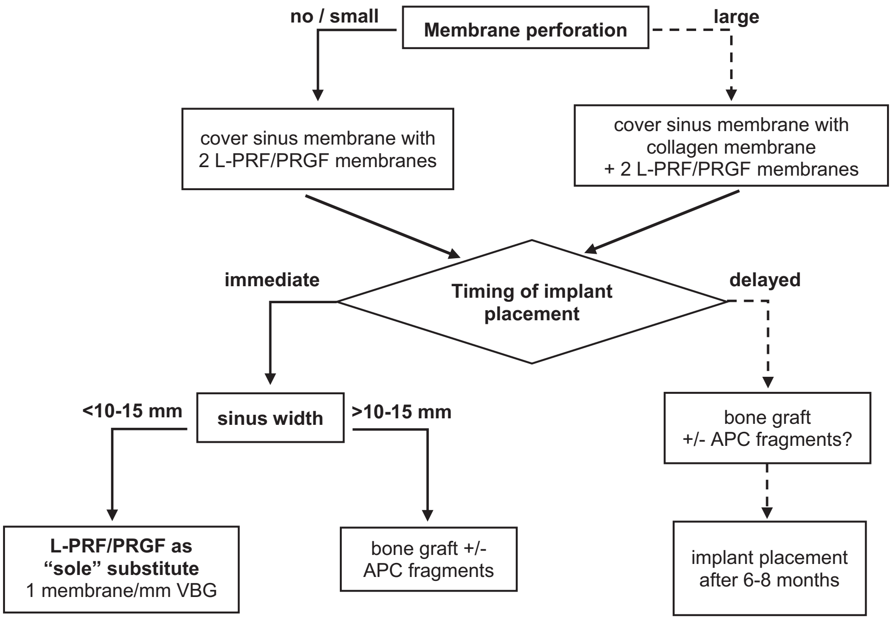


5.2.3 | Lateral window approach for sinus floor elevation

In case of sufficient and/or good bone quality to place an implant simultaneous with a one-stage lateral window sinus lift, L-PRF membranes can serve as "sole" substitute offering around 5 mm VBG (range reported = 3.4–10.4 mm). The amount of RBH does not seems to play a significant role. Avila and co-workers[103] however identified the bucco-palatal width of the sinus as a potential limitation for the use of L-PRF alone. They reported that a lateral sinus augmentation with an allograft in narrow or medium sinuses (<15 mm in width) gave roughly three times more vital bone after 6-months of healing when compared to wide sinuses (>15 mm). Therefore, it could be proposed that for sinuses wider than 15 mm, the combination with a bone substitute is preferred.

The decision tree below, (adapted from[104]), might help the clinician in when to use L-PRF. For PRGF and PRP, no studies were found supporting their use as "single" substitute.

The addition of APCs to a bone substitute during a two-stage lateral window approach only slightly improved the amount of newly formed bone, especially at the early stage (4 months).



As such, this review supports the use of APCs, and specifically of L-PRF in transcrestal and one-stage lateral window sinus lift, also taking the following additional benefits into consideration: lower cost, better PROMs, the 100% autogenous nature, and the fact that it is user-friendly.

CONFLICT OF INTEREST STATEMENT

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

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