Do Recombinant, Purified, and Concentrated Growth Factors Enhance the Regenerative Potential of Particulate Bone Graft Substitutes in Maxillary Sinus Floor Augmentation? A Systematic Review and Meta-analysis

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Purpose: To answer the following question: "Do recombinant, purified, and concentrated growth factors enhance the regenerative potential of particulate bone graft substitutes in maxillary sinus floor augmentation (MSA)?" ***Materials and Methods:*** Human studies comparing histomorphometric data on new bone formation, residual graft material, and fibrous tissue ratio (outcomes of interest) following MSA procedures employing particulate bone grafts/substitutes in combination or not with growth factors were retrieved from PubMed/MEDLINE, Web of Science, Cochrane, and Scopus online databases and complemented with a hand search. Controlled studies published in English up to December 2022 and reporting on histomorphometric data expressed as volume percentage of the outcomes of interest were considered. Risk of bias was assessed, and a meta-analysis was performed to investigate the effects of supplementary growth factors on new bone formation, remaining graft particles, and fibrous tissue ratio. ***Results:*** Data were included from 613 samples in 477 patients reported in 22 publications. Meta-analysis showed that platelet-rich plasma or platelet-rich fibrin resulted in 49% more new bone formation than in control group areas ($P = .004$), and those areas supplemented with growth factors presented 57% less residual graft particles after healing ($P < .0001$). A significant ($P = .03$) 1.85-fold increase in connective tissue formation was noted in areas treated with recombinant human bone morphogenetic proteins (rhBMPs) after healing. ***Conclusions:*** Selective supplementary growth factors may enhance new bone formation and accelerate particulate graft turnover, while rhBMP may significantly increase connective tissue formation in MSA procedures in humans. *Int J Oral Maxillofac Implants 2024;39:e87–e101. doi: 10.11607/jomi.10553*

Keywords: bone grafts, bone morphogenetic proteins, growth factors, histomorphometry, sinus elevation

Progressive bone loss after tooth extractions and increased maxillary sinus pneumatization are major causes of insufficient bone volume at the edentulous posterior maxillary areas,[1] presenting challenges for treatment with implant-supported prostheses. Therefore, bone regenerative techniques, such as maxillary sinus augmentation (MSA) procedures, were developed to increase bone height and effectively support dental implants in the partially and fully edentulous posterior maxilla.[2] Well-documented, positive, short-[2,3] and long-term[4–6] clinical results have been reported for MSA procedures applying several types of graft materials[2,3,7] in conjunction with the lateral window approach (LWA). However, despite the widespread use[7] and reported successful outcomes,[2–6] an important limitation of the procedure is the significant healing time, usually longer than 6 months, for enhanced bone formation, particularly when materials other than autogenous bone are employed.[5]

Even though the osteoconductive properties[9–11] and lack of osteoinduction and osteogenesis[12] of bone substitutes (BGS) have been well documented, the ideal graft material for sinus augmentation is still a matter of controversy,[13] and there is still a search for optimal biomaterial combinations to enhance bone regeneration. In an attempt to enhance the osteogenic potential of BGS in MSA procedures, the addition of autogenous bone grafts was suggested,[14] but no significant improvement was noted.[15] New therapies based on local delivery of bioactive substances offer a new paradigm in bone reconstructive therapy as a resource to amplify or accelerate the endogenous healing potential. These therapies employ either growth factors (GFs) obtained through the concentration or purification of biologic

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Table 1 Search Strategy for Medline via PubMed

Search terms used
((((((((((human[MeSH Terms]) OR humans[MeSH Terms]) OR human[Title/Abstract]) OR humans[Title/Abstract]) OR man[Title/Abstract]) OR male[Title/Abstract]) OR woman[Title/Abstract]) OR female[Title/Abstract])) AND (((((Sinus floor augmentation[MeSH Terms]) OR Sinus floor augmentation[Title/Abstract]) OR Sinus augmentation[Title/Abstract]) OR Sinus floor elevation[Title/Abstract]) OR sinus lift[Title/Abstract])) AND ((((((((((((((((((((((Growth factor[MeSH Terms]) OR Growth factor[Title/Abstract]) OR prp[Title/Abstract]) OR Platelet-rich plasma[Title/Abstract]) OR emd[Title/Abstract]) OR Emdogain[Title/Abstract]) OR Enamel matiz derivate[Title/Abstract]) OR prf[Title/Abstract]) OR Platelet-rich fibrin[Title/Abstract]) OR rhPDGF[Title/Abstract]) OR platelet-devived growth factor[Title/Abstract]) OR GEM 21S[Title/Abstract]) OR Growth-factor enhanced matrix[Title/Abstract]) OR PDGF BB[Title/Abstract]) OR platelet-devived growth factor BB[Title/Abstract]) OR INFUSE[Title/Abstract]) OR rhBMP-2[Title/Abstract]) OR recombinant human bone morphogenetic protein-2[Title/Abstract]) OR bone morphogenetic protein-2[Title/Abstract]) OR recombinant proteins[Title/Abstract]) OR rhGDF-5[Title/Abstract]) OR (recombinant human growth[Title/Abstract] AND differentiation factor-5[Title/Abstract])) OR growth differentiation factor-5[Title/Abstract]) OR GDF5 protein[Title/Abstract])) AND (((((Histomorphometric[MeSH Terms]) OR Histomorphometric[Title/Abstract]) OR New bone formation[Title/Abstract]) OR Residual graft areas[Title/Abstract]) OR Histovolumetric[Title/Abstract])

materials (autogenous or xenogeneic) or recombinant DNA technology that act at the cellular and molecular levels to enhance bone regeneration. Therefore, mixing the graft material with a biologic modifier including GFs may reduce the healing time and enhance osteoinductive process of new bone formation.[14] These GFs may include autogenous platelet concentrates preparations, enamel matrix derivative (EMD), recombinant human platelet-derived GF (rh-PDGF), recombinant human bone morphogenetic protein (rhBMP), and recombinant human growth and differentiation factor (rhGDF).

The hypothesis under consideration is that the use of GFs increases or accelerates bone regeneration following MSA procedures. Therefore, the present systematic review (SR) aims to evaluate histomorphometric data on new bone formation, residual graft material, and fibrous tissue ratio as potential regenerative effect measurements derived from the addition of different GFs to BGS on MSA procedures. This evaluation hopes to answer the following question: "Do recombinant, purified and concentrated GFs enhance the regenerative potential of particulate bone graft substitutes in maxillary sinus floor augmentation?"

MATERIALS AND METHODS

Protocol Registration

The protocol of this SR was registered in PROSPERO (no. CRD42019117738). There was no deviation from the originally specified protocol as registered. The basic methodology of the present study followed the recommendations of the PRISMA checklist,[16] the PRISMA-P 2015 Statement for Systematic Reviews,[17] and the Cochrane Handbook for Systematic Reviews of Interventions.[18] The focused question for the search strategy was constructed using the PICOS (population, intervention, comparison, outcome, study design) strategy.[19]

Focused Question

The focused question for this SR is: In patients who received bone grafts loaded with GFs for maxillary sinus floor augmentation, what is the histomorphometric pattern of this neoformed bone when compared to the control group?

Search Strategy

An electronic systematic search without date or language restriction was carried out in PubMed/Medline, Web of Science, and Scopus databases for studies published up to December 10, 2022. Furthermore, a specific electronic search was performed on the following journal websites: *Journal of Periodontology*, *Journal of Clinical Periodontology*, *Clinical Oral Implants Research*, *Clinical Implant Dentistry and Related Research*, *The International Journal of Oral & Maxillofacial Implants*, *International Journal of Oral & Maxillofacial Surgery*, and *Implant Dentistry*. A search of the Grey Literature Report[20] and OpenGrey databases[21] revealed unpublished studies (grey literature). The reference lists of the included studies (cross-referencing) were also searched.

MeSH terms, keywords, and other free terms were used with Boolean operators (OR) to combine searches. The search strategy included appropriate changes in the keywords and followed the syntactic rules of each database. The search strategy for Medline via PubMed is shown in Table 1.

Inclusion and Exclusion Criteria

Patients were included in the study according to the PICOS strategy.

- Population: healthy adults (≥ 18 years old, male or female) who received sinus floor augmentation
- Interventions: Maxillary sinus floor augmentation with bone substitutes supplemented with GFs
- Comparison: Bone substitutes without the addition of GFs

- Outcome: Amounts of newly formed bone, remaining graft particles, and ratio of fibrous tissue
- Study design: Randomized clinical trials and clinical trials

The following exclusion criteria were applied: abstracts, letters to editors, narrative reviews, case reports or series, insufficient/unclear data precluding data extraction, and lack of author response for data clarification.

Screening Process

The search and screening process was carried out by two independent reviewing authors (V.V.M. and R.B.S.), starting with analysis of titles and abstracts. In the second step, full papers were selected for careful reading and analyzed according to eligibility criteria for future data extraction. Studies were included if they met the following criteria: *(1)* used bone graft alone compared to bone graft loaded with GFs; *(2)* performed a quantitative histomorphometric analysis of the outcome variables (amounts of newly formed bone, remaining graft particles, and fibrous tissue ratio); *(3)* calculated the volume occupied by the variable over the total volume, indicating the fraction of volume (percentage) occupied by the variable of interest (BV/TV%); and *(4)* presented the results as means and SDs. Covariates such as age, gender, duration of operation, and others were not evaluated due to lack of standardization in the reporting. Disagreements between reviewing authors were resolved through careful discussion.

Risk of Bias Assessment

Cochrane's tool for assessing the risk of bias and Review Manager (RevMan) software (version 5.4, Cochrane Collaboration) were used. The study analyses were performed according to the following parameters: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias.

Each parameter was classified as yes (low risk of bias), no (high risk of bias), or unclear when the information could not be found. The reviewers performed the analysis independently, and the final decision was made with consensus. The risk of bias was classified according to the answers received as follows: 1 to 2 "no" marks = high risk; 3 to 7 "yes" marks = low risk; and 4 to 7 "unclear" marks = medium risk.

Data Extraction

When available, the following data were extracted from the included studies by two independent reviewers (V.V.M. and R.B.S.): authors, number of patients evaluated, mean age, sinus elevation technique, bone graft used, GF used, dosage, biopsy time and technique, newly formed bone, residual graft particles, fibrous tissue formation, financial interest, and conclusion of test group.

Statistical Analysis

The meta-analysis was performed with the guidelines of the Cochrane handbook for Systematic Reviews of Interventions[18] employing the weighted mean differences and 95% CI data for the means and SDs obtained at the histomorphometric evaluations, with the RevMan statistical software package. Forest plots were used to illustrate the outcomes of the meta-analyses. Mean prediction intervals and their 95% lower and upper limits were only calculated and reported for meta-analyses including at least three studies.

$P \leq .05$ was considered statistically significant (Z-test). Intrastudy heterogeneity was assessed with the v2-based Q test, and interstudy heterogeneity was evaluated with the I^2 inconsistency test.[22] The I^2 value ranged from 0 to 100, with values > 50% indicating substantial heterogeneity, and values > 75% suggesting high heterogeneity.[23] Significant heterogeneity was indicated by $P < .1$ because of the moderate insensitivity of the Q statistic.[24] Due to expected interstudy heterogeneity, a random effect model (DerSimonian and Laird model) was used. The "one study removed" test was performed when there was moderate or high heterogeneity. The test was performed to detect whether any particular study influenced the heterogeneity.

RESULTS

Literature Search

The initial search resulted in 384 titles from Medline/PubMed, 543 from Web of Science, and 480 from Scopus. After removing duplicate studies, 743 records remained for abstract screening. After this first evaluation, 53 complete articles remained. After critical reading, 31 studies were excluded because they did not meet the eligibility criteria. Thus, 22 studies[25–46] were included in the present SR. A search of grey literature did not result in any additional studies. The article search and selection process is shown in Fig 1.

Study Characteristics

The characteristics of the included studies are presented in Table 2. All studies were published between 2005 and 2021. The main age of patients ranged from 36 to 61 years old. Of the 22 included clinical trials, 3 were multicenter studies, and 13 realized a split-mouth design. The open lateral window technique was used by all authors

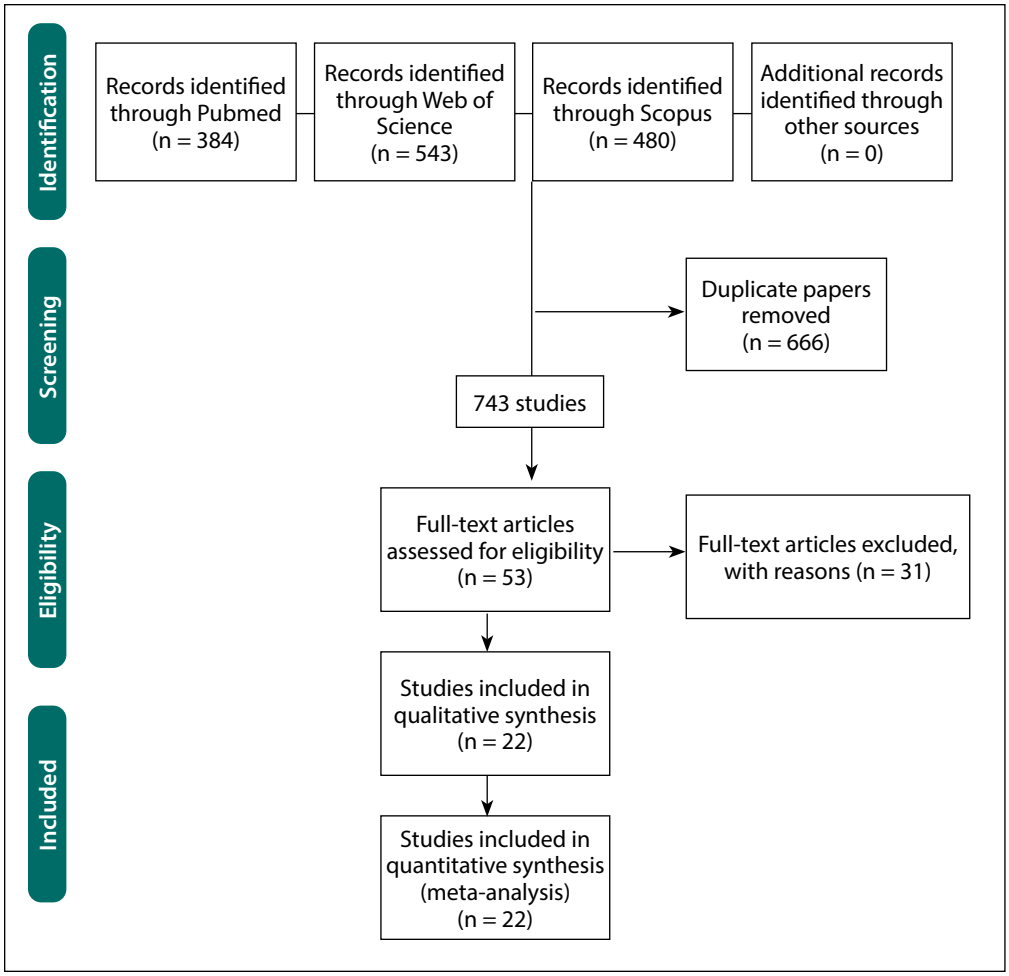

Fig 1 Flowchart of the study selection process.

for sinus elevation. Bone material, GF, and the dosages varied in each study: 13 clinical trials used bovine graft, 2 used autologous bone, 4 used synthetic substitute, and 3 used allograft bone. The most frequently tested GFs were platelet-rich fibrin (PRF; 7 studies), platelet-rich plasma (PRP; 5 studies), rhBMP (5 studies), EMD (2 studies), bone marrow cells (2 studies), PDGF (1 study), and rhGDF-5 (1 study). Only one study tested 2 different GFs (PRF and PRP). The majority of authors used a trephine burr to collect the biopsy specimen at implant placement. The bone regeneration period ranged from 3 to 9 months. Furthermore, all clinical trials evaluated newly formed bone, 21 evaluated remaining graft particles, and 16 evaluated fibrous tissue ratio in histomorphometric analysis. Within the studies, the 9 groups that presented an accelerated tissue transformation are the ones that collected the biopsy sample earlier (3 to 4 months), except for 4 studies that collected the sample at 6 months. The other 17 groups did not reveal any differences between test and control specimens.

Meta-analysis

A meta-analysis was performed with the 22 included clinical trials. Figure 2 summarizes a global analysis combining results from all bioactive treatments for new bone formation. The meta-analysis demonstrated that new bone formation was not significantly increased in areas supplemented with GFs when compared to control groups without GFs (Mean: 0.23; 95% CI: –0.03 to 0.46; $P = .09$); however, moderate ($I^2 = 61\%$), significant (v2 = 0.30; $P < .00001$) heterogeneity was observed between studies.

The secondary data analysis for new bone formation with individual GFs when associated with bone grafts in sinus floor augmentation procedures is presented in Fig 3. Subgroup analysis comparing bioactive treatments showed that areas of bone grafts loaded with either PRP or PRF (Fig 3a) presented significantly more bone formation than areas in control groups without these GFs (MD: 0.51; 95% CI: 0.11 to 0.90; $P = .01$). Once again, significant (v2 = 0.21; $P = .004$), moderate

(I^2 = 48%) heterogeneity was observed between studies. Interestingly, areas treated with bone grafts supplemented with PRP (Fig 3b) presented significantly more bone formation than areas in control groups without these GFs (MD: 0.78; 95% CI: 0.18 to 1.38; *P* = .01), while grafts supplemented with PRF (Fig 3c) did not (MD: 0.27; 95% CI: –0.22 to 0.76; *P* = .16). Moderate (I^2 = 51%), nonsignificant (v2 = 0.24; *P* = .08) heterogeneity was observed between studies with PRP (see Fig 3b). Similarly, studies with PRF demonstrated low (I^2 = 36%), nonsignificant (v2 = 0.13; *P* = .16) heterogeneities.

Three[34,45,46] out of six studies reported enhanced new bone formation after supplementing bone grafts with PRP. These studies used autogenous illiac grafts (AIG)[34,45] or a freeze-dried bone allograft (FDBA).[46] Even though moderate (I^2 = 37%), nonsignificant (v2 = 0.15; *P* = .16) heterogeneity was noted for the six studies employing PRP, three studies[32,43,45] showed only minimal, nonsignificant enhancement of bone formation following the use of PRP in conjunction with either a bovine xenograft (BOVX)[43] or a β-tricalcium phosphate (β-TCP) graft.[32] One study[45] reported that PRP significantly stimulated bone formation only in areas grafted with AIG at 3 months while no significant difference was noted after 6 months of healing. Interestingly, one study[32] compared the combination of a β-TCP graft with either PRF and PRP and reported that while PRP was minimally stimulatory, PRF was inhibitory. Three studies reported doses of 1:1[46] or smaller[45,32] proportions of PRP to graft volume, while two studies[32,43] did not adequately report the PRP dosage used.

Three[26,28,41] out of seven studies[25,26,29,30,32,41,28] employing PRF preparations in conjunction with bone grafts/substitutes reported enhanced new bone formation. Three studies used BOVX,[28,29,41] two studies used a demineralized bone matrix allograft (DBMA),[25,30] and two studies[26,32] used a β-TCP material. While low (I^2 = 39%), nonsignificant (v2 = 0.15, *P* = .13) heterogeneity was observed for seven studies employing PRF, only two studies[26,28] showed significant, increased new bone formation favoring PRF, while another study[41] showed only minimal, nonsignificant bone formation enhancement following the use of PRF in conjunction with a bovine xenograft. No significant enhancement in new bone formation was noted for the use of PRF in conjunction with either a DBMA[25,30] or BOVX, but an effect on new bone formation was reported when PRF was used in conjunction with a β-TCP graft.[32] Two studies reported bigger doses[28,32] and one a smaller dose[29] than a 1:1 proportion of PRF to graft volume, while three studies[25,30,41] did not adequately report the PRP dosage used.

Several purified or recombinant GF preparations were tested for effect on enhancing particulate bone graft/substitutes in sinus elevation procedures, including EMD,[27,31] rhBMP-2,[35,36,40,42] rhBMP-7,[37] rhPDGF,[39] and rhGDF-5.[44] BOVX was supplemented with rhBMP,[37,42] EMD,[27] and rhPDGF.[39] Biphasic hydroxyapatite/β-TCP (HA/β-TCP) was supplemented with either rhBMP[36] or EMD,[31] while mineralized cancellous bone allograft (FDBA)[40] and hydroxyapatite (HA)[35] were supplemented with rhBMP. The potential effects of supplemental recombinant human GFs in augmenting bone formation in areas grafted with bone substitutes are presented in Fig 4. The global analysis results of the meta-analysis performed combining all 12 included clinical trials (Fig 4a) did not show significant increases in new bone formation in areas supplemented with purified/recombinant GFs when compared to control groups without GFs (MD: 0.06; 95% CI: –0.51 to 0.39; *P* = .80); however, high (I^2 = 75%), significant (v2 = 0.44; *P* < .00001) heterogeneity was observed between studies. Secondary analysis for new bone formation with individual GFs showed that incorporating rhBMP-2, rhBMP-7, rhPDGF, rhGDF-5, or EMD to particulate bone substitutes did not significantly enhanced bone formation.

The secondary data analysis for new bone formation after different healing times following sinus floor augmentation procedures are presented in Fig 5. Subgroup data analyses obtained after 3 to 4 months of healing (Fig 5a) showed that there were positive (MD: 0.39; 95% CI: –0.17 to 0.95), nonsignificant (*P* = .17) effects of GFs on early bone formation; however, high (I^2 = 77%), significant (v2 = 0.58; *P* ≤ .0001) intra- and interstudy heterogeneities were observed. Data obtained after 6 months of healing (Fig 5b) revealed that despite the low intra- and interstudy heterogeneities (v2 = 0.07; *P* = .16, I^2 = 25%), no significant differences among treatments could be demonstrated (MD: 0.11; 95% CI: –0.13 to 0.35; *P* = .38).

Figure 6a summarizes a global analysis combining results from all of the bioactive treatments for residual bone graft particles and demonstrates that, despite the significant (v2 = 0.28; *P* < .0001), moderate (I^2 = 58%) heterogeneity observed between studies, areas supplemented with GFs presented significantly less residual graft particles after healing (MD: –0.57; 95% CI: –0.84 to –0.31; *P* < .0001).

The secondary data analysis for residual bone graft particles in areas treated with recombinant (rhBMP-2, rhBMP-7, rhPDGF, rhGDF-5, EMD) or enriched (PRP/PRF) GFs are presented in Figs 6b and 6c, respectively. Subgroup data analyses revealed significantly reduced amounts of residual graft particles in areas treated with either recombinant (MD: –0.71; 95% CI: –1.14 to –0.27; *P* = .001) or enriched (MD: –0.48; 95% CI: –0.83 to –0.13; *P* = .008) GFs, despite the significant (v2 = 0.39; *P* < .0001), high (I^2 = 71%) heterogeneity observed among studies employing recombinant GFs. Interestingly, areas treated with enriched GFs revealed

Table 2 Characteristics of Included Studies

No.	Authors	No. of patients evaluated (test/control)	Mean age	Study	Sinus lift technique	Residual alveolar crest height in the maxillary sinus (mm)	Graft
1	Adah et al (2021)	10 (10/10)	57	RCTSM	OLW	1 – 3	DBMA
2	Cinar et al (2020)	20 (10/10)	53	RCT	OLW	< 5	β-TCP
3	Vincent-Bugnas et al (2020)	8 (8/8)	59	RCTSM	OLW	N/R	BBBM
4	Pichotano et al (2019)	12 (12/12)	54	RCTSM	OLW	< 4	BBBM
5	Batas et al (2019)	6 (6/6)	N/R	RCTSM	OLW	N/R	BBBM
6	Nizam et al (2018)	13 (13/13)	50	RCTSM	OLW	< 5	BBBM
7	Nery et al (2017)	10 (10/10)	55	RCTSM	OLW	3 – 5	β-TCP/HA
8	Comert Kiliç et al (2017)	26 (9/8/9)	36	RCTSM	OLW	< 7	β-TCP(S)
9	Oliveira et al (2016)	15 (7/7/7)	55.4	RCT	OLW	< 4	BBBM
10	Badr et al (2016)	22 (13/9)	36	RCT	OLW	N/R	Iliac crest
11	Kim et al (2015)	127 (65/62)	53	RCTM	OLW	N/R	BBBM
12	Kim et al (2015) b	42 (23/23)	52	RCTM	OLW	N/R	BBBM
13	Corinaldesi et al (2013)	9 (9/9)	50	RCTSM	OLW	N/R	BBBM
14	Wildburger et al (2013)	7 (7/7/7)	58	RCTSM	OLW	< 3	BBBM
15	Froum et al (2013)	24 (12/12/12)	61	RCTSM	OLW	< 4 – 5	BBBM
16	Froum et al (2013) b	32 (11/10/11)	N/R	RCTSM	OLW	< 4 – 5	MCBA
17	Zhang et al (2012)	10 (6/5)	43	RCT	OLW	< 5	BBBM
18	Kao et al (2012)	22 (11/11)	50.8	RCT	OLW	< 5	BBBM
19	Cabbar et al (2011)	10 (10/10)	53	RCTSM	OLW	< 5	USBG
20	Stavropoulos et al (2011)	31 (11/10/10)	53	RCTM	OLW	< 5	(A)(B)β-TCP or (C) β-TCP + ABC
21	Thor et al (2007)	11 (11/11)	55	RCTSM	OLW	N/R	Iliac crest
22	Kassolis et al (2005)	10 (10/10)	N/R	RCTSM	OLW	5	FDBA

ABC = autologous bone chips harvested from the mandibular angle; APRS = azur and pararosanilin; AT = autogenous thrombin; β-TCP/HA = BoneCeramic; β-TCP(S) = β-TCP/Suprabone; BBBM = Bio-Oss bovine graft; BMC = bone marrow cells; DBMA = Tissuelab allograft/demineralized bone matrix allograft; EMD = Emdogain; GPF = Gieson's picro-fuchsin; GT = Goldner's trichrome; H1 = trephine bur at upper end of the implant via lateral window; H2 = distal and superior area of the previous window site; H3 = between the superior and inferior position of the lateral window osteotomies; HE = hematoxylin and eosin; ICBMC = bone marrow cells including mesenchymal stem cells harvested from the posterior iliac crest; LA = longitudinal axis; LLS = Levai-Laczko stain; L-PRF1 = membrane fragments (4–5 mL) mixed with 0.5 g of Bio-Oss small granule; L-PRF2 = membrane fragments mixed with 1.5 g of DBBM large granule; MCBA = mineralized cancellous bone allograft; MT = Masson's trichrome; N/R = not reported; OLW = open lateral window; PRGF = platelet-rich growth factor; PS = paragon stain; PSHE = picrosirius-hematoxylin; RCT = randomized clinical trial; RCTM = RCT multicenter; RCTSM = RCT split-mouth; SB = Stevenel blue; TB = toluidine blue; USBG = Unilab Surgibone bovine graft; VGPF = Van Gieison's picro fuchsin.

Growth factor	Dosage	Time for biopsy implant installation (months)	Biopsies technique	Lamina stains
PRF membranes	N/R	6	Longitudinal axis	Hematoxylin and eosin
PRF	N/R	6	Longitudinal axis	Hematoxylin and eosin
EMD	N/R	6	Longitudinal axis	Paragon stain
L-PRF membranes	Fragments of membrane (4-5 mL) mixed with 0.5 g of Bio-Oss small granule	4 (test) 8 (control)	Longitudinal axis	Hematoxylin and eosin
PRGF	0.5 mL PRGF mixed with 1 cc of DBBM small granule	6	N/R	Gieson's picrofuchsin
L-PRF membranes	Fragments of membrane mixed with 1.5 g of DBBM large granule	6	Longitudinal axis	Goldner's trichrome
EMD	1 g of BoneCeramic for 0.3 mL of EMD + NaCl 0.9%	6	Longitudinal axis	Picrosiriushematoxylin
(A) P-PRP (B) PRF	(A) 2 mL P-PRP mixed with 2 mL β-TCP (B) 4-5 mL PRF mixed with 2 mL β-TCP	6	Longitudinal axis	Hematoxylin and eosin
BMC (A) single centrigugation (B) double centrifugation	N/R	6	Longitudinal axis	Hematoxylin and eosin
PRP sprayed on the cancellous bony chips	N/R	3 – 4	Longitudinal axis	Toluidine blue
rhBMP-2/H (Novosis-Dent)	N/R	4	Trephine bur at upper end of the implant (via lateral window)	N/R
ErhBMP-2/BCP (Cowell BMP)	N/R	6	Longitudinal axis	Hematoxyline and eosin and Masson's trichrome
rhBMP-7 Osigraft (eptotermin)	3.5 mg in collagen 1 g	4	Bucal side	N/R
ICBMC	MSC(3mL) + BBBM (2g)	(A) 3 (B) 6	Longitudinal axis	Azur and Pararosanilin
rhPDGF	0.5 mL of PDGF 0.3 mg/mL with 5g DBBM	(A) 4 – 5 (B) 7 – 9	Distal and superior area of the previous window site	Stevenel blue and Van Giesison picro fuchsin
rhBMP-2	(A) MCBA + 5.6 mL rhBMP-2/ACS (8.4 mg rhBMP-2) (B) MCBA + 2.8 mL rhBMP-2/ACS (4.2 mg rhBMP-2)	6 – 9	Between the superior and inferior position of the latral window osteotomies	Stevenel blue and Van Giesison picro fuchsin
PRF	N/R	6	Alveolar crest	Levai-Laczko stain
rhBMP-2/ACS	rhBMP-2 + ACS/BBM 80/20 ratio	6 – 9	N/R	Toluidine blue
PRP	N/R	6	Longitudinal axis	Toluidine blue
rhGDF-5	(A)(B) 500 µg rhGDF-5/g β-TCP mixed with 0.9% NaCl (C) 1:1	(A) 3 (B) 4 (C) 4	Longitudinal axis	N/R
PRP	3 mL PRP to 1 mL of autogenous thrombim	(A) 3 (B) 6	Longitudinal axis	1% toluidine blue mixed with 1% pyronin-G
PRP	4 mL PRP to 5 cc FDBA	4.5 – 6	Longitudinal axis	Hematoxylin and eosin

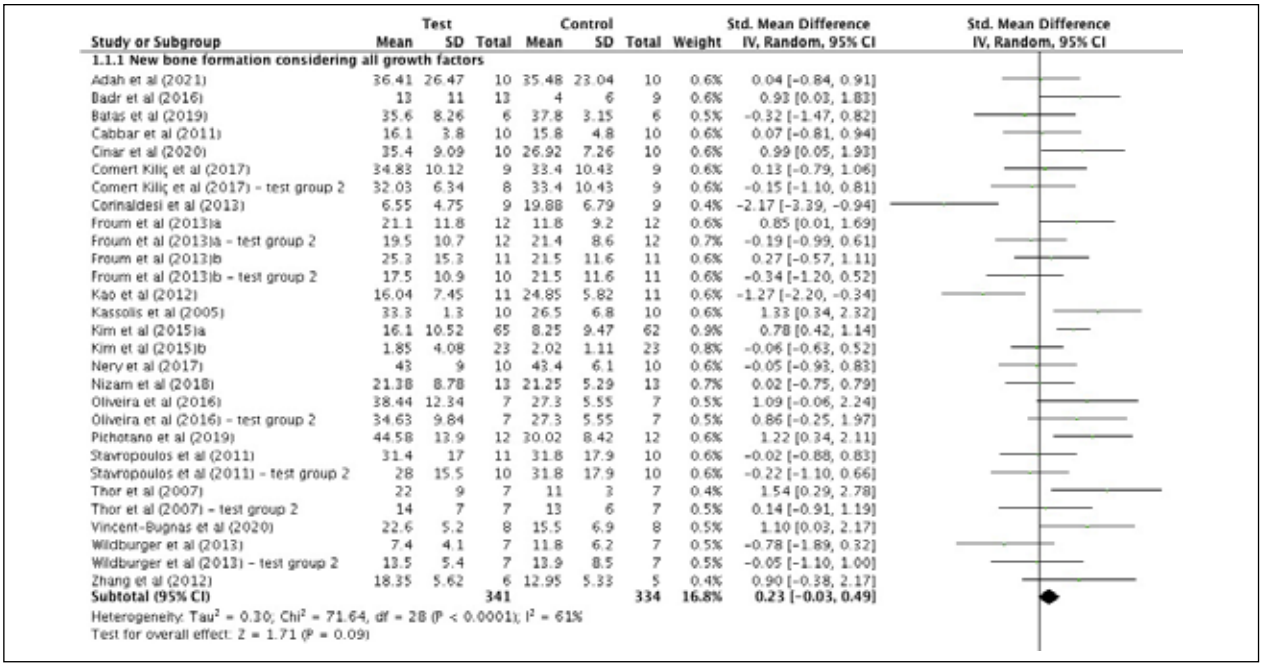

Fig 2 Forest plot analysis for new bone formation, comparing sinus floor augmentation with different GFs when associated with bone grafts.

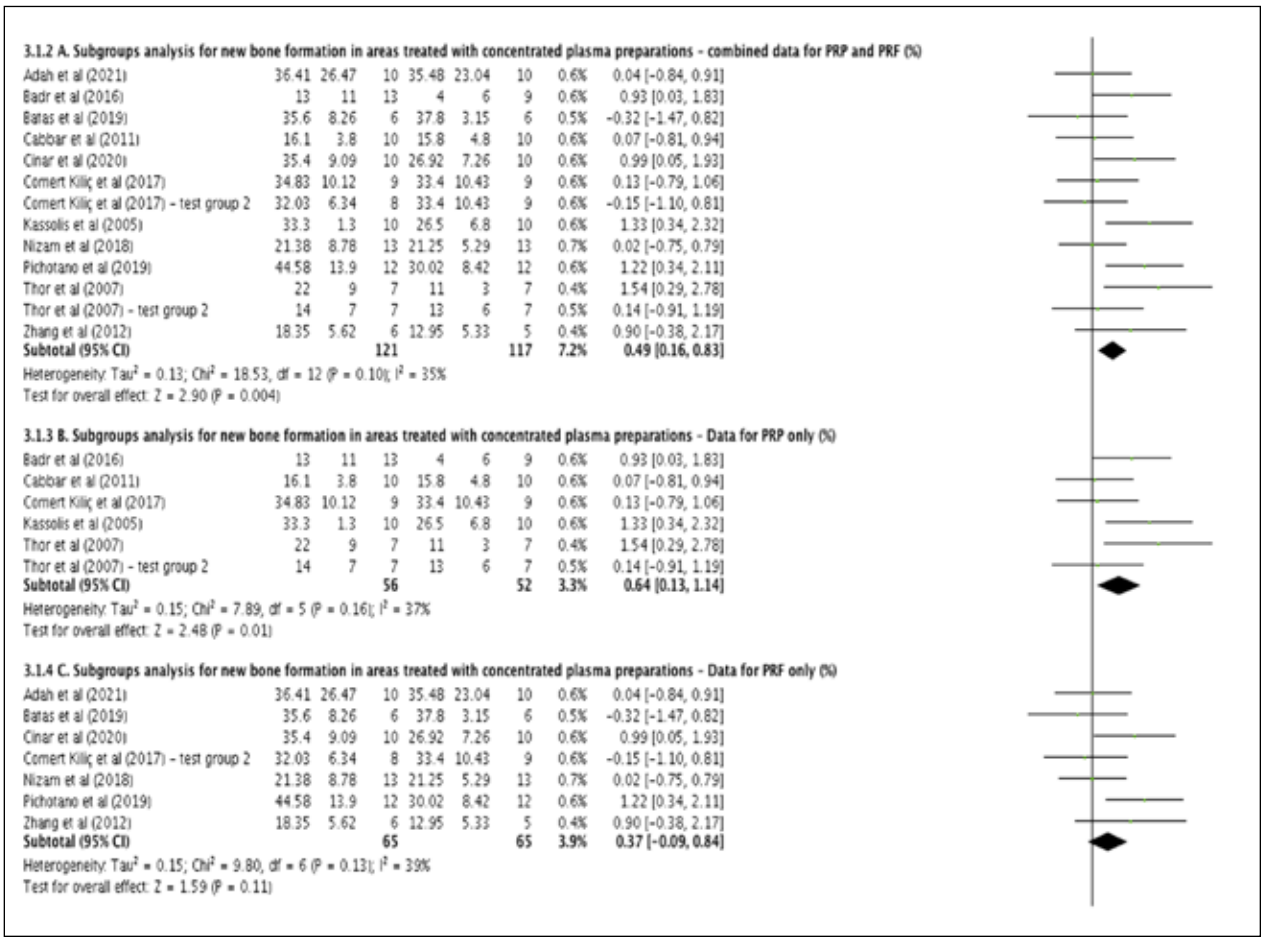

Fig 3 Forest plot analysis for new bone formation, comparing sinus floor augmentation with bone grafts enriched with GFs to concentrated plasma preparations. *(a)* Overall effects of PRP and PRF. *(b)* Effects of PRP only. *(c)* Effects of PRF only.

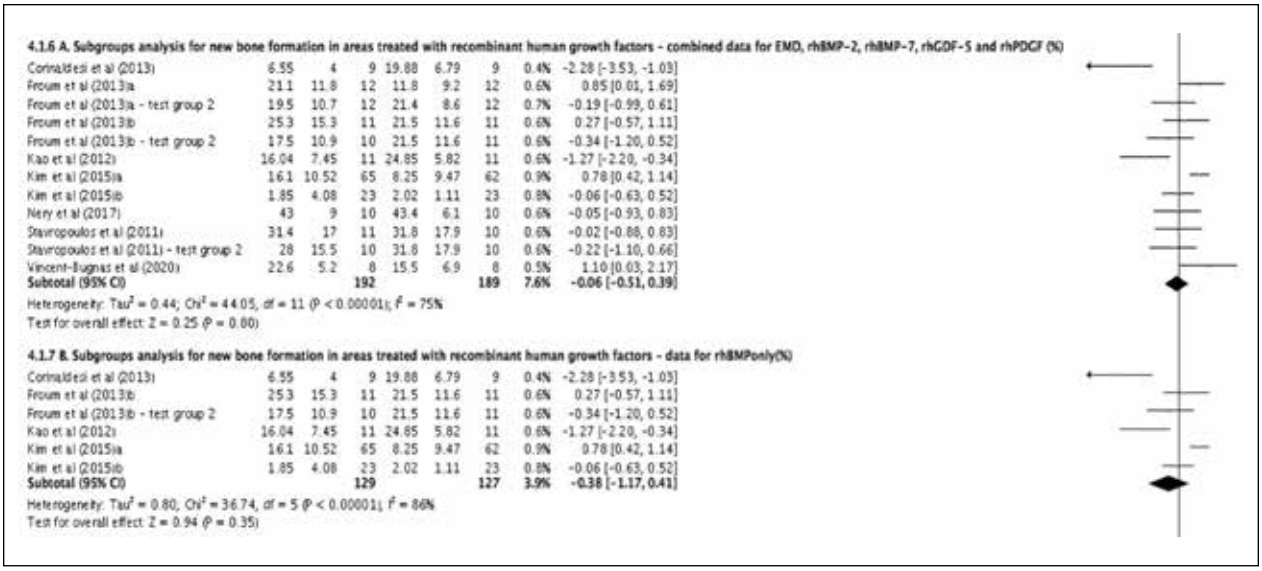

Fig 4 Forest plot analysis for new bone formation, comparing sinus floor augmentation to bone grafts enriched with recombinant GFs. *(a)* Global effects of for EMD, rhBMP-2, rhBMP-7, rhDGF-5, and rhPDGF. *(b)* Effects of rhBMP-2 only.

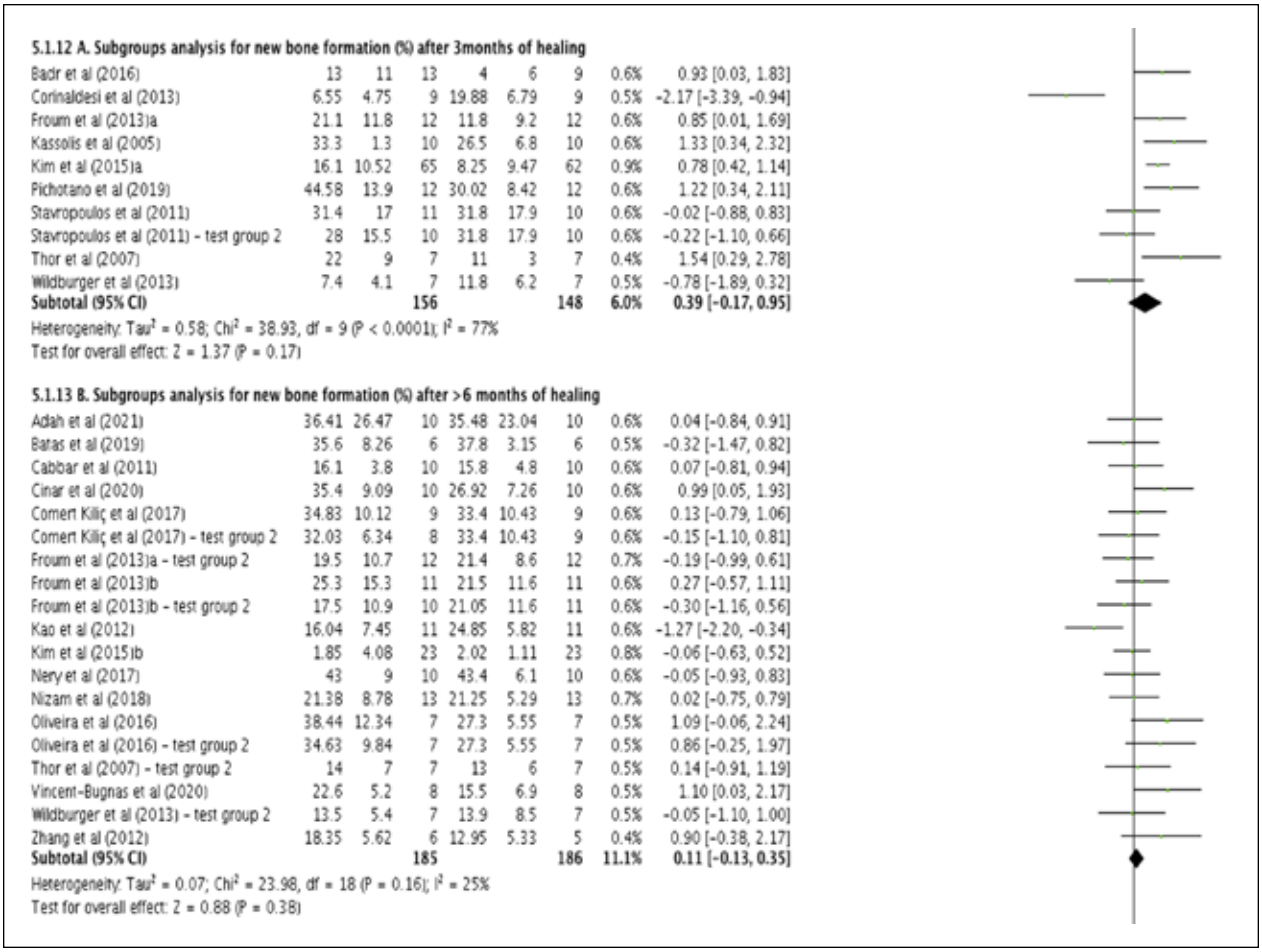

Fig 5 Forest plot analysis for new bone formation, comparing sinus floor augmentation with healing times associated with bone grafts. *(a)* Subgroup analysis for new bone formation (%) after 3 months of healing. *(b)* Subgroup analysis for new bone formation (%) after > 6 months of healing.

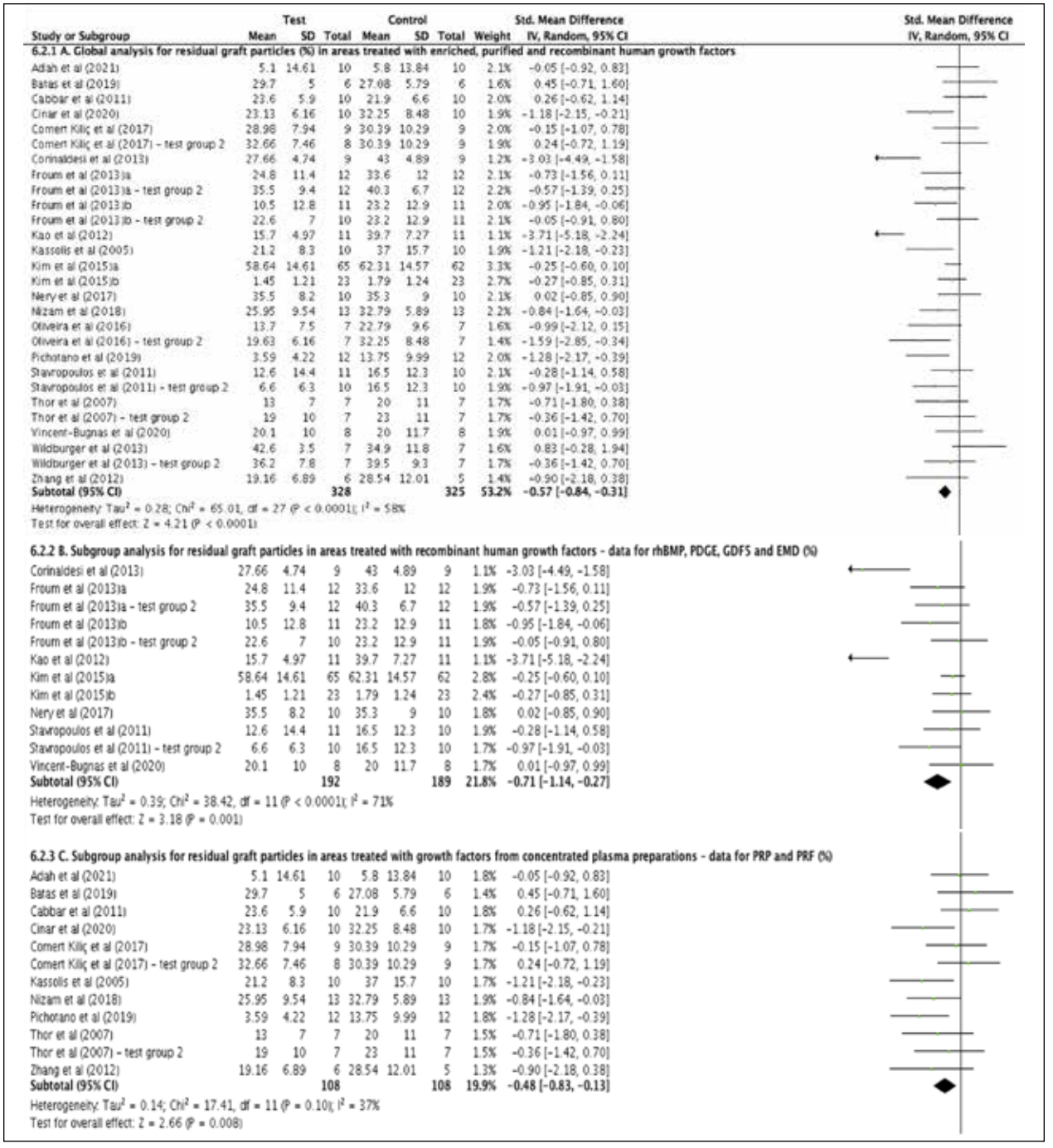

Fig 6 *(a)* Forest plot analysis for residual bone graft particles, comparing sinus floor augmentation with different GFs when associated with bone grafts. *(b)* Effects for rhBMP-2, rhBMP-7, rhPDGF, rhGDF-5, and EMD. *(c)* Effects for PRP/PRF.

nonsignificant (v2 = 0.14; *P* =.10), low (I^2 = 37%) heterogeneity.

Figure 7a summarizes a global analysis combining results from all of the bioactive treatments for connective tissue formation and demonstrates that areas supplemented with GFs did not significantly alter the amount of soft connective tissue formation in comparison with areas in control groups without GFs (MD: 0.24; 95% CI: −0.13 to 0.61; *P* = .20); however, moderate (I^2 = 73%), significant (v2 = 0.47; *P* < .00001) heterogeneity was observed between studies. Interestingly, subgroup data analyses revealed significantly increased (MD: 1.85; 95% CI: 0.15 to 3.55; *P* = .03) connective tissue formation after healing in areas treated with rhBMP (Fig

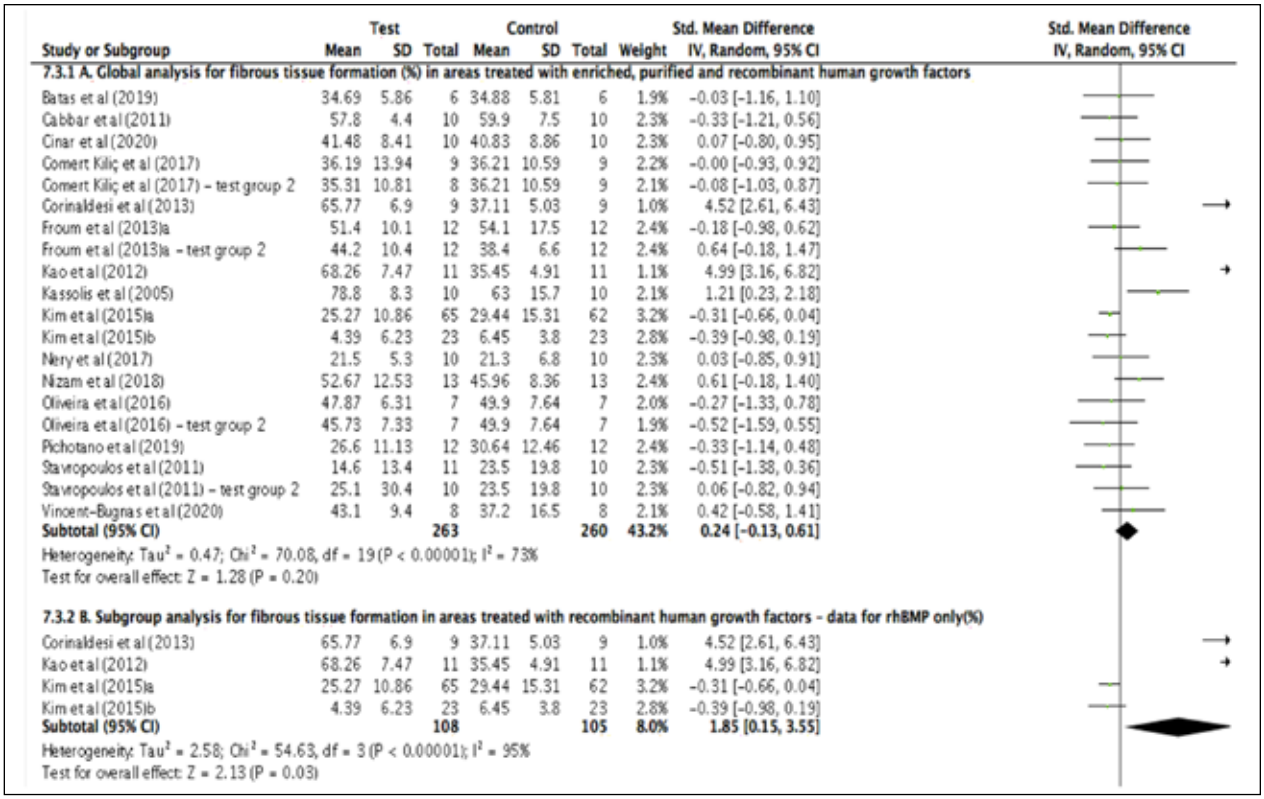

Fig 7 Forest plot analysis for connective tissue formation, comparing sinus floor augmentation with different GFs when associated with bone grafts. *(a)* Global analysis. *(b)* Effects for BMP only.

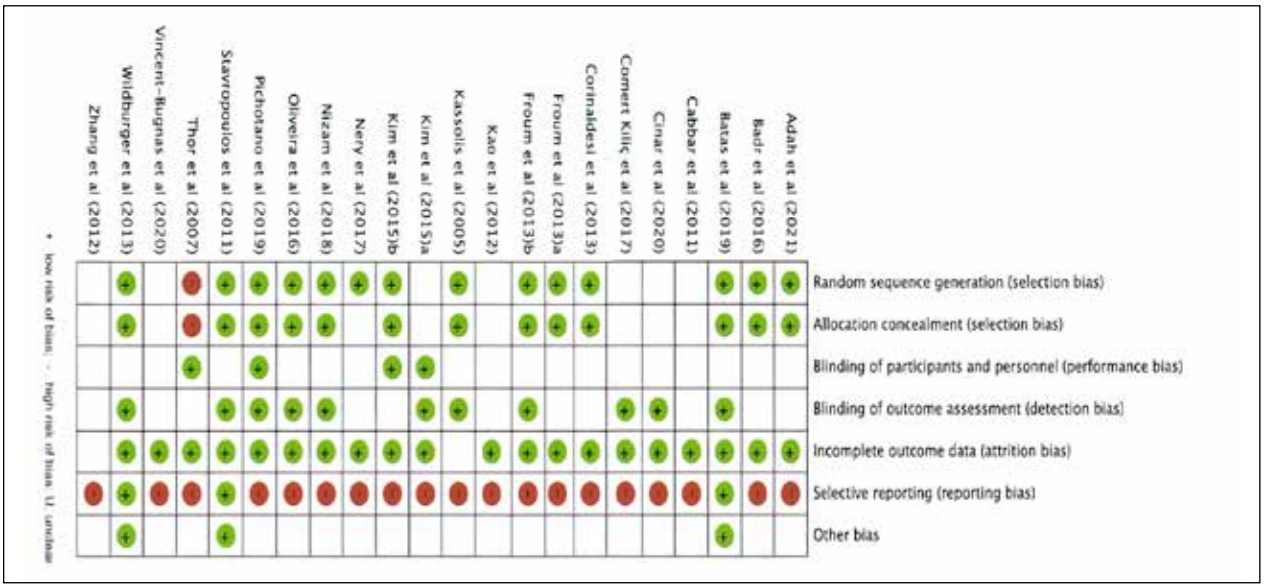

Fig 8 Risk of bias analysis.

7b); however, significant (v2 = 2.58; $P < .00001$), high ($I^2 = 95\%$) heterogeneity was observed for the amount of connective tissue formation among the studies employing rhBMP.

Risk of Bias of Included Studies

The results of risk of bias assessment for included RCTs is summarized in Fig 8. In total, 14 studies were considered to have a low risk of bias; 7 studies were considered to have a moderate risk of bias, and 1 study was considered to have a high risk of bias.

DISCUSSION

Summary of Evidence

Selective GFs may positively influence the regenerative effects of bone substitutes in sinus elevation procedures by augmenting bone formation and reducing the amount of residual bone substitute material, possibly as a result of accelerated or increased bone formation and increased turnover of graft particles. The present SR demonstrated that these potential enhancements of the regenerative effects of bone substitutes supplemented with GFs is a complex and multifactorial phenomenon that appears to be influenced by the type and dosage of the GF and the type of bone graft used.

Effects of GFs on New Bone Formation

The existing evidence analyzed herein showed that several concentrated, purified, or recombinant GF preparations were tested for the enhancement of particulate bone graft/substitutes in sinus elevation procedures, including: PRP[32,34,43,45,46]; PRF[25,28,29,30,32,41]; EMD[27,31]; rhBMP[235,36,40,42]; rhBMP-7[37]; rhPDGF[39]; and rhGDF-5.[44] The present SR showed that, among all of the GFs tested so far, only PRP significantly increased new bone formation when mixed with particulate bone grafts/substitutes (MD: 0.78; 95% CI: 0.18 to 1.38; $P = .01$).

Even though nonsignificant (v2 = 0.15; $P = .16$) moderate ($I^2 = 37\%$) heterogeneity was noted for the five studies employing PRP, three[34,45,46] studies employing AIG[34,45] or FDBA[46] as the graft material, reported enhanced new bone formation after supplementing bone grafts with PRP. One of these studies[45] and the remaining two studies[32,43] showed only minimal, nonsignificant, enhancement on bone formation following the use of PRP in conjunction with either BOVX[43] or β-TCP graft.[32] One study[45] reported that PRP significantly stimulated early bone formation and had no significant effects on late bone formation in areas grafted with AIG. Interestingly, one study[32] compared the combination of a β-TCP graft with either PRF and PRP and reported that while PRP was minimally stimulatory, PRF was inhibitory. Therefore, the available evidence suggests a potential additive effect of PRP to either autogenous or allogenous bone grafting, while nonsignificant outcomes were obtained with a BOVX or a β-TCP graft. PRP appears to accelerate bone formation in areas grafted with AIG rather than increasing the total amount of bone formed in late osteogenesis.

Interestingly, several doses of PRP were tested in relation to the volume of particulate graft material. Three studies reported 1:1[46] or smaller[32,45] proportions of PRP to graft volume, while two studies[32,43] did not adequately report the PRP dosage used. Thus, it seems that proportions of 1:1 (or smaller) of PRP to particulate graft appear to be more effective than higher doses, particularly if autogenous bone or DFDBA are used, while not significantly enhancing new bone formation in conjunction with synthetic materials such as a β-TCP graft. Future studies must strive to adequately and carefully report the PRP dosages and proportions to bone graft/substitute volume employed to maintain protocol consistency among studies and allow for meaningful data comparison.

Even though no significant enhancement in bone formation was noted in areas supplemented with recombinant GFs, there is some evidence that rhBMP could enhance new bone formation when used in conjunction with a particulate bone graft/substitute under certain conditions; however, significant (v2 = 0.03; $P < .0001$), high ($I^2 = 88\%$) heterogeneity is observed between studies. Two types of BMPs were tested (rhBMP-2[35,36,40,42] and rhBMP-7[37]) in conjunction with either BOVX,[37,42] HA,[35] 70:30 HA/β-TCP biphasic composite,[36] or FDBA[40] as carriers. Two studies showed a significant enhancement of new bone formation by using 0.5 to 2.0 mg of rhBMP-2 in conjunction with an HA carrier[35] or 1.0 mg of rhBMP-2 to 1 g of a 70:30 HA/β-TCP biphasic carrier.[36] Interestingly, two arms of one study[40] did not show significant differences for different doses (8.4 or 4.2 mg) of rhBMP-2 added to FDBA. Paradoxically, two studies[37,42] showed a significant inhibitory effect of rhBMP on new bone formation following grafting with a BOVX. One study[37] used 3.5 mg of rhBMP-7 in 1 g of a collagen carrier, while another study mixed rhBMP-2 in an acellular collagen sponge with a xenograft in an 80/20 ratio. In contrast to the results reported for PRP, the available evidence demonstrated that significantly enhanced new bone formation was only reported when rhBMP-2 was used in conjunction with synthetic carriers such as HA[35] or a biphasic 70:30 HA/β-TCP material.[36]

Other purified or recombinant GF preparations (such as EMD,[27,31] rhPDGF,[39] and rhGDF-5[44]) were also evaluated in sinus elevation procedures employing BOVX,[39,27] biphasic HA/β-TCP,[31] or monophasic β-TCP[44] as carriers. Two studies showed a significant enhancement of new bone formation 4 to 5 months after rhPDGF[39] or 6 months after EMD[27] was mixed with BOVX. No significant difference in new bone formation was noted after 3 to 4 months of healing when rhGDF-5 was mixed with monophasic β-TCP,[44] after 6 months when EMD was mixed with biphasic HA/β-TCP material,[31] and after 7 to 9 months when rhPDGF was mixed with BOVX.[39] Accelerated new bone formation in grafted sinuses may occur by combining rhPDGF with BOVX[39] or rhGDF with monophasic β-TCP,[44] as no differences in new bone formation were noted 3 to 4 months after rhGDF/monophasic β-TCP[44] nor between 4 to 5 months and 7 to 9 months of healing after rhPDGF/BOVX.[39] Interestingly, in contrast to the results reported for PRP

and rhBMP-2, the available evidence demonstrated that significantly enhanced new bone formation was reported when BOVX was used in conjunction with rhPDGF[39] or 6 months after EMD.[27]

Effects of Healing Time on New Bone Formation Enhancement by GFs

To evaluate whether GFs could enhance the regenerative potential of particulate bone grafts/substitutes by accelerating new bone formation, a secondary data analysis was performed for new bone formation after different healing times following sinus floor augmentation procedures. The global analysis of data herein showed that no significant differences were observed after 3 to 4 or ≥ 6 months of healing; however, despite the increased treatment effect of 39% for new bone formation with GF supplementation after 3 to 4 months of healing, significant (v2 = 0.58; $P \leq .0001$), high ($I^2 = 77\%$) heterogeneity was observed between studies. In contrast, although no significant differences among treatments could be demonstrated (MD: 0.11; 95% CI: –0.13 to 0.35; $P = .38$), low, nonsignificant heterogeneities (v2 = 0.07; $P = .16$; $I^2 = 25\%$) were observed for studies with ≥ 6 months of healing.

Interestingly, a positive (MD: 0.75; 95% CI: 0.18 to 1.33), significant ($P = .06$) effect of PRP on early bone formation was documented in the subgroup analysis of data obtained after 3 to 4 months of healing. Thus, it appears that the potential benefits of supplementary GFs on bone formation in grafted human sinuses is highly variable and manifested during the earlier stages of bone healing. After 6 months of healing, the amount of vital bone is similar in areas treated with and without GFs. These data seem to suggest that supplementary GFs may have the potential to accelerate bone healing rather than enhance the total amount of bone formation, with the exception of PRP, which could do both. Moreover, a minimum healing period of 6 months after grafting is suggested in order to reduce biologic variability and increase the clinical reproducibility of new bone formation in sinus elevation procedures, even when GFs are employed.

Effects of GFs on Residual Bone Graft Particles

Ideally, the resorption rate of a bone graft/substitute should be matched to the formation rate of new bone tissue until the grafted bone is completely replaced with new vital bone tissue. The presence of bone graft substitute (BSB) residual grafted particles after bone healing may lead to the formation of a composite repair tissue rather than a regenerated bone tissue.[47] The global data analysis of the present SR showed that GF supplementation resulted in significantly less residual graft particles than in control group areas using grafting biomaterials alone (MD: –0.51; 95% CI: –0.80 to –0.23; $P < .0004$); however, significant (v2 = 0.29; $P < .0001$), moderate ($I^2 = 61\%$) heterogeneity was observed between studies. These effects were noted with recombinant (rhBMP) or enriched (PRP/PRF) GF preparations. However, a significant (v2 = 0.83; $P < .00001$), high ($I^2 = 86\%$) heterogeneity was observed between studies using rhBMP, while areas treated with PRP or PRF demonstrated moderate ($I^2 = 42\%$), nonsignificant ($v^2 = 0.16$; $P = .08$) heterogeneity between studies. Thus, enriched autogenous GF preparations (PRP/PRF) appear to consistently increase turnover of graft particles, resulting in significantly reduced residual bone substitute material.

Effects of GFs on Connective Tissue Formation

Among the GFs used to supplement bone grafts/substitutes, only rhBMP significantly increased (MD: 1.85; 95% CI: 0.15 to 3.55; $P = .03$) connective tissue formation after healing, despite the significant (v2 = 2.58; $P < .00001$), high ($I^2 = 95\%$) heterogeneity observed. These results are consistent with previous radiographic data, suggesting that sinuses grafted with FDBA supplemented with rhBMP-2 had a reduced bone density compared to control sites grafted with FDBA alone.[48]

Clinical Applications and Considerations

Enriched autogenous GF preparations (such as PRP) enhance bone regeneration when added in a 1:1 (or smaller) proportion to particulate AIG[34,45] or FDBA,[46] possibly by accelerating bone formation in grafted areas rather than increasing the total amount of bone formed in late osteogenesis.[45] PRP and PRF also increase the turnover of graft particles, resulting in significantly reduced residual bone substitute material after healing, leading to proportionally increased amounts of mineralized vital bone in grafted sinuses.

Enhanced bone regeneration was noted in sinuses grafted with BOVX mixed with either rhPDGF[39] or EMD[27]; however, increased bone formation was detected earlier (4 to 5 months of healing) in sinuses grafted with rhPDGF[39] than those grafted with EMD (6 months),[27] suggesting that rhPDGF may accelerate bone formation in grafted sinuses.[39] These substances did not have significant effects on the amounts of residual graft particles and connective tissue formation after healing.

The potential additional benefits of supplementary rhBMP to particulate BGS in MSA procedures is a complex interplay of grafting material type and dose and the type of BMP employed. Significant enhancements in bone regeneration were only reported when rhBMP-2 was used in conjunction with synthetic carriers such as HA[35] or a biphasic 70:30 HA/β-TCP biphasic carrier[36]; no effects were noted when rhBMP-2 was combined with FDBA[40]; and an inhibitory effect was

reported with BOVX.[37,42] Effective doses were 0.5 to 2.0 mg of rhBMP-2 with HA[35] and 1.0 mg of rhBMP-2 to 1 g of HA/β-TCP.[36] Moreover, rhBMP supplementation resulted in decreased amounts of residual graft particles and increased connective tissue formation, possibly resulting in reduced bone density compared to control sites grafted with particulate bone grafts alone.[48] Therefore, the combined effects of reduced amounts of residual graft particles and increased connective tissue formation following the addition of rhBMP question its usefulness for MSA in conjunction with particulate BGS.

Strengths and Weaknesses of the Study

The present SR systematically evaluated the results of 22 studies on the effects of concentrated, purified, and recombinant GFs on the enhancement of particulate BGS in MSA. Six biologically active preparations (PRF, PRP, rhBMP, EMD, PDGF, and rhGDF-5) were combined with bovine xenograft, autologous bone, synthetic substitutes, or allograft bone and compared with the BGS alone. These substances and biomaterials are frequently used in clinical practice, and thus the present results can provide evidence-based recommendations for current clinical practice and future investigations. Despite the significant number of studies evaluated, uncertainties in the calculating of point estimates from primary studies with different study designs and employing a plethora of grafting protocols may explain the overall high heterogeneity for new bone formation. Unfortunately, evidence was either limited or controversial for several BGS and GF combinations, thus limiting more definitive considerations on ideal material/biologic selection protocols.

Future studies must strive to adequately and carefully report the GF dosages and proportions to bone graft/substitute volume employed to maintain protocol consistency among studies and achieve meaningful data comparisons. Moreover, an adequate selection of healing times, particularly earlier than 6 months of healing, is also recommended to evaluate potential accelerated bone regeneration with selective GF/particulate biomaterial combinations.

CONCLUSIONS

Enhancing the regenerative effects of particulate bone grafts/substitutes with supplemental GFs is a complex and multifactorial phenomenon that appears to be influenced by the GF type and dosage, the bone graft type, and the postsurgical healing time. Specific combinations (such as bone auto/allograft + PRP, BOVX + rhPDGF or EMD) and selective monophasic/biphasic synthetic BGS + rhBMP appear to enhance bone regeneration in grafted sinuses. The positive influence of selective GFs (such as PRP, rhPDGF, EMD, and rhBMP-2) on the regenerative effects of BGS in MSA procedures appears to be exerted by augmenting bone formation and reducing the amounts of residual bone substitute material, possibly because of accelerated or increased bone formation and increased turnover of graft particles. These findings provide evidence-based guidelines that may help clinicians select the appropriate tissue engineering strategies for enhanced new bone formation in sinus grafting with particulate bone substitutes.

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