Clinical Efficacy of Growth Factors to Enhance Tissue Repair in Oral and Maxillofacial Reconstruction: A Systematic Review

Henning Schliephake, MD, DDS, PhD

ABSTRACT

Purpose: Provide a comprehensive overview on the clinical use and the efficacy of growth factors in different reconstructive procedures in the oral maxillofacial area.

Materials and Methods: A systematic review of the literature on the clinical use of human and human recombinant growth factors in oral maxillofacial reconstruction has been performed.

Results: The use of autogenous growth factors in platelet concentrates (PCs) has shown to be beneficial in the treatment of intrabony pockets at a reasonable level of evidence by improving probing depth and clinical attachment levels as well as linear bone fill within the limits of the observation periods. The application in conjunction with non-autogenous graft materials has been superior to the use of PCs only or grafting materials alone. No benefits have been shown for the use of PCs in recession treatment. When used in furcation treatment, probing depth, clinical attachment level and linear bone fill have been reported to improve significantly, however, without clinical benefit. No benefit for the final outcome could be shown for the use of PCs neither in sinus lift procedures nor in lateral / vertical crest augmentations. The use of human recombinant growth factors has been so far limited almost exclusively to rhPDGF-BB and rhBMPs (BMP-2, BMP-7 and GDF-5). The use of rhPDGF in the treatment of intrabony pockets has shown a reliable increase in linear bone fill but weaker evidence for permanent improvements of clinical attachment level. So far there is no evidence to support the use in recession treatment, sinus lift procedures and socket healing as well as lateral / vertical augmentations of the alveolar crest. rhBMPs have shown to be effective in enhancing bone formation in socket healing (rhBMP-2) and sinus lift procedures (rhBMP-2 and GDF-5). No controlled studies are available for the use in mandibular segmental repair. Successful reports on this application appear to be limited to primary reconstruction after ablative surgery for benign pathology with preservation of the periosteum.

Conclusion: Evidence of clinical efficacy of growth factors in reconstructive procedures in the oral and maxillofacial area is limited.

KEY WORDS: bone regeneration, bone tissue engineering, extraction socket, maxillary sinus floor elevation, platelet-rich fibrin, randomized controlled trial

INTRODUCTION

Growth factors are part of a system of signals that coordinate wound healing and tissue repair. The identification of individual players and the increasing understanding of their roles in this process have fostered the idea of using growth factors not only to enhance tissue repair in compromised sites but also to induce tissue regeneration to fill defects and build up new tissue in order to obviate tissue transfer. This imagination has elicited countless research efforts to develop strategies and modes of application that would allow clinicians to use growth factors for regenerative purposes.

Growth factors convey signals to their target cells through receptor binding, which results in activation of specific target genes. The number and the nature of activated target genes determine the cellular response. The site-specific dose relation and sequence of different growth factors thereby contributes to the quality and

Professor and chairman, Abteilung für Mund-, Kiefer-und Gesichtschirurgie, Georg-August-Universität, Göttingen, Germany

Reprint requests: Prof. Henning Schliephake, Dept Oral Maxillofac Surg, George Augusta University, Goettingen, Germany; e-mail: schliephake.henning@med.uni-goettingen.de

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quantity of tissue regeneration. As several types of cells are involved in tissue repair, interaction of several growth factors is required for successful tissue regeneration.

The identification of the genetic code of growth factors has enabled the production of human recombinant proteins more than 20 years ago. This has repeatedly raised hopes that effective clinical application is just around the corner. Unfortunately, despite extensive research and successful preclinical testing, the clinical use of human recombinant growth factors has not yet reached a level of application that would reflect the numerous successful experimental reports that have been published for more than 15 years. Costs and regulatory issues as well as the complexity of mimicking physiological dosage levels at the site of delivery have rendered the introduction of human recombinant growth factors into clinical use more difficult than it has been anticipated.[1]

An alternative strategy that has been applied more frequently than the application of recombinant proteins is the use of patients' own growth factors. Autogenous growth factors are present in rather large quantities in platelets and are easily available from platelet enriched centrifugation products of whole blood. Different concepts and preparation methods have been developed, that vary in the content of platelets, leukocytes and fibrin and hence the condition of application (liquid vs. gel) (for review see Dohan Ehrenfest and colleagues[2]).

Platelet concentrates (PCs) contain a combination of growth factors that are listed in Table 1. The concentration may vary between individual patients and according to the method of production.[3–5] The growth factors are contained in the alpha granules of the platelets. They can be released by addition of calcium chloride, allogeneic thrombin or by autologous fibrin depending on the preparation technique.[2,3,6–10] Other than individual recombinant growth factors, PCs convey a number of signals that may vary in their relative strength according to the dose levels present in the individual preparations. According to the nature of the growth factors contained in PCs, they are supposed to enhance mesenchymal and epithelial proliferation as well as angiogenesis. The use of autogenous proteins is hardly impaired by regulatory issues and is available at low costs. The ease of production and the almost unrestrained use has fuelled a widespread clinical application of PCs in regenerative procedures.[11,12]

Both the use of autogenous growth factors in PCs and the application of human recombinant growth factors have produced a multitude of reports on different indications at different levels of evidence that is difficult to manage for the clinical practitioner. It was therefore felt desirable to provide a comprehensive overview on the clinical use and the efficacy of growth factors of both origins in different reconstructive procedures in the oral maxillofacial area in a systematic review.

MATERIALS AND METHODS

Conduct and reporting of the present systematic review has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13]

Search Strategy

A search strategy was set up for an electronic search in PubMed libraries and the Cochrane library from 1995 to 2012. The search terms used were the following: *growth factors*, *PRP*, *platelet rich*, *platelet concentrates*, *PDGF*, *platelet-derived growth factor*, *FGF*, *fibroblast growth factor*, *EGF*, *epithelial growth factor*, *VEGF*, *vascular endothelial growth factor*, *TGF*, *transforming growth factor*, *BMP*, *bone morphogenic protein* in combination with *clinical*, *dental*, *oral*, *maxillary*, *maxillofacial*, *mandibular*, *periodontal*, *regeneration*, *reconstruction*, *study*, and *trial*. Moreover, hand search of the following journals from the period 1995 (or the earliest available issue) to 2012 was done: *International Journal of Oral and Maxillofacial Surgery*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Craniomaxillofacial Surgery*, *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Clinical Oral Implant Research*, *International Journal of Oral Maxillofacial Implants*, *Clinical Implant Dentistry and Related Research*. Additionally, reference lists from systematic reviews and meta-analyses were screened.

TABLE 1 Growth Factor Content of Platelet Concentrates[3–5]

PDGF-BB	TGF-β	b-FGF	VEGF	EGF	IGF-I
ng/ml[3,5]	ng/ml[3,5]	pg/ml[3]	ng/ml[3]	ng/ml[3,4]	ng/ml[161,401,402]
2.3–233.0	6.2–268.0	3,5–95.0	0.1–0.7	0.1–1.6	5.9–112.0

Screening and Eligibility

The electronic search generated 4665 papers: hand search had produced 121 studies. Excluding duplications 4611 references were identified. The papers not previously identified by hand search were screened by title and all experimental reports or papers deemed irrelevant for other reasons (prior research, research on vaccination and transfusion, oncologic research, monoclonal antibody research) that could be identified at this stage were excluded by title. If there was doubt about the relation to the search topic, the abstract was considered. All studies that reported the clinical use of autogenous and human recombinant growth factors in the oral maxillofacial and craniofacial area were included. Papers on the use of animal-derived growth factor extracts were not considered. The resulting 427 papers were screened by abstract, and 180 more papers were excluded due to preclinical research studies ($n = 7$), use of nonhuman growth factor extracts ($n = 3$), and clinical applications outside of the oral and maxillofacial (OMF) area such as plastic surgery, orthopedic/trauma surgery, gynecology, ophthalmology, and endocrinology ($n = 173$). The remaining 244 clinical reports were grouped into five levels of evidence: case reports and case series, cohort studies without controls, cohort studies with controls, randomized controlled trials (RCTs), and systematic reviews/meta-analyses. To discriminate between case series and cohort studies, a full text analysis was done and only papers with defined criteria for case inclusion and outcome parameters were considered as cohort studies.

During the screening process it became obvious that the use of growth factors in certain applications has been reported almost exclusively through case series and noncontrolled cohort studies. Although it is not common to include noncontrolled studies in a systematic review, it was decided to keep case reports, case series, and cohort studies without controls in the evaluation because a large area of expertise in the use of recombinant growth factors would have been lost to the readers if all noncontrolled reports would have been excluded from this analysis. In order to avoid potential sources of bias through the inclusion of noncontrolled studies, controlled and noncontrolled studies are clearly identified in the report and considered separately.

Data Evaluation

In general, methods and reporting of the results were very heterogeneous with respect to both details and quality, which impaired quantification and systematic comparison of the effect of all growth factor applications in a meta-analysis. In order to analyze the large variety of papers, the report was structured according to the growth factors used and the analysis was performed separately for the different indications broken down into the levels of evidence. Case reports/case series as well as cohort studies without controls were reported using only a brief descriptive summary for each indication.

Cohort studies with controls and RCTs were submitted to analysis of quantitative results whenever possible. As a systematic comparison of all numeric results in a meta-analysis fashion was not feasible for the above-mentioned reasons, two levels of comparison of individual outcome parameters were selected and applied were appropriate:

Ratio of Significance. If outcome parameters have been reported to a reasonable degree of homogeneity across the studies involved, a ratio was calculated for each of these parameters from the number of studies that reported significant results in favor of the tested growth factor in relation to the number of studies that had evaluated this parameter. This ratio ranged between 0 and 1 and thus indicated the strength of significance of the individual outcome parameter documented by the studies involved. In bone augmentation procedures (sinus lift procedures, lateral/vertical augmentation procedures, cleft repair, and segmental reconstruction) lack of significant differences compared with controls was also considered as positive if autogenous bone had been used as controls. When more than one period of evaluation had been used, the results of the longest observation period were included. The required degree of homogeneity in outcome variable reporting has not been achieved in all applications.

Numerical Values. If metric values of outcome parameters in individual applications have been assessed at a comparable level of methodology across the respective studies, differences in weighted means were used to compare treatments and calculated as percentage of controls. Metric values were presented as absolute values and as percentage of the controls. Dimensionless values (e.g., implant stability quotient ISQ) and radiographic scores were presented only as percentage of the controls in order to minimize potential bias due to differences in assessment methods.

Potential bias on the study level and the outcome level was considered separately for the individual indications in the Results section, as the quality of the individual studies varied grossly across the different applications of growth factors.

RESULTS

The overall number of papers on the use of growth factors for tissue repair in oral and maxillofacial surgery has considerably increased over the past 15 years (Figure 1). The majority of papers ($n = 163$) reported the use of PCs. In terms of evidence level, controlled studies and RCTs constituted the majority of reports ($n = 126$) compared with 103 descriptive studies such as case reports and case series as well as cohort studies without controls. Fifteen systematic reviews/meta-analyses could be identified. Despite a remarkable increase in the number of controlled studies and RCTs, the proportion of controlled studies in relation to total number of studies per year has not changed substantially over time.

Autogenous Growth Factors/PCs

Three types of PCs have been used: platelet-rich plasma (PRP) ($n = 137$), platelet-rich fibrin (PRF) ($n = 18$), and plasma/preparation rich in growth factors (PRGF) ($n = 8$). PCs had been produced using commercially available kits in 26 reports, the remaining studies had used individual standardized centrifugation protocols.

The largest number of studies of PCs have been published on implant site development ($n = 69$) including sinus floor augmentation ($n = 42$), followed by socket healing ($n = 15$) and lateral/vertical augmentations ($n = 12$). The second most frequent indication have been applications in regenerative periodontal treatment ($n = 63$: intrabony pockets: $n = 51$; recession treatment: $n = 9$; furcation treatment: $n = 3$) (Table 2). It is obvious that the number of controlled studies in periodontal indications was almost four times as high as the noncontrolled reports, whereas this ratio was much lower in sinus floor augmentations and also in socket healing procedures. A rather new area of application has shown to be endodontic treatment ($n = 10$). The remaining applications that have been reported for the use of PCs are characterized either by a higher number of noncontrolled studies or a small number of reports available.

Implant Site Development

Sinus Floor Augmentation/Noncontrolled Studies. Three case reports,[14–16] nine case series[17–25], and five cohort studies without controls[26–30] on the use of PCs for enhancement of bone formation in sinus lift procedures have been identified. Three reports had employed PRF,[17–19] the remaining studies had applied PRP. The majority of studies had used bovine bone mineral, allogenic bone or autogenous bone as carriers. Two studies on the application of PRF[17,19] had used fibrin blocks only without additional grafting materials to fill the subsinus cavity. One study[25] reported a negative outcome with loose connective tissue and only limited amounts of newly formed bone between the graft particles. The

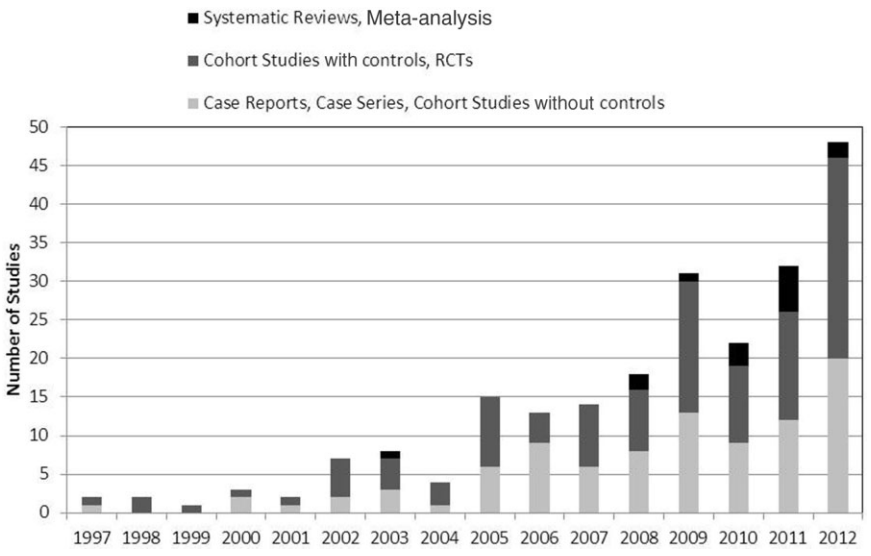

Figure 1 Development of the level of evidence of published articles on the clinical use of growth factors from 1997–2012.

TABLE 2 Studies on Platelet Concentrates (PCs) According to Level of Evidence and Indication (Reference Numbers)

Indication		Case Reports Case Series Cohort Studies without Controls			Cohort Studies w Controls RCTs			Systematic Reviews, Meta-Analyses
		PRP	PRF	PRGF	PRP	PRF	PRGF	
Periodontology	Intrabony pockets	85–91,93,94	92		78–82,95,99,100,102–124	83,96–98,101		11,12,247–249
	Recession	84			126,130–132	127–129	125	
	Furcation				133,134	135		
Sinus floor augmen.		14–16,20–30	17–19		31–33,35–43,45–50	44	34	250–254
Socket healing		53–55	51,52		56,57,59–64		58,65	
Lat. / vert. augm.		66–75			76,77			
Endodontics		136,138,140,142	143,144	145	137,139,141			
BRONJ / ORN		151		149,150	152–154			
Implant stability					146–148			
Segmental reconstr.		155,156			157			
Cosmetic surgery		158					159	
Cyst cavity healing					160,161			
Wound healing		163			162			
Fracture					164			
CLP					165			
Distraction osteogenesis		166						

remaining studies described uneventful healing and satisfactory bone formation with subsequent stable anchorage of dental implants.

Sinus Floor Augmentation/Cohort Studies with Controls, RCTs. Fourteen cohort studies with controls[31–44] and 6 RCTs[45–50] were available for evaluation. Seventeen of these studies had used PRP and one each had used PRF and PRGF, respectively. Autogenous bone had been used as carrier in 6 studies and allogeneic bone in 2 reports. Xenogenic grafting material had been employed in 6 reports and synthetic material in only two. The heterogeneity of evaluation methods and outcome parameters employed prevented the analysis of the effect of the grafting material on results. All in all 373 patients had been included into these studies. Observation periods after the use of PCs in sinus lift procedures ranged from 5 to 96 months.

The average gain in bone formation derived from 5 histologic studies was 16.1% in favor of PCs.[33,37,40,42,43] A significant increase in new bone formation (NB) had been found after a minimum of 5–6 months of healing in only 1/5 studies (Figure 2). The mean increase in histologic bone density (bone quality/BQ) calculated from 9 studies was 6.2% higher in the test groups.[34–36,38,41,45,46,48,49] A significant increase had been observed in 3/9 studies. Differences in radiologic bone density (BD) changes after sinus lift procedures were derived from 6 studies[38,41,44,45,48,50] and averaged 6.5%

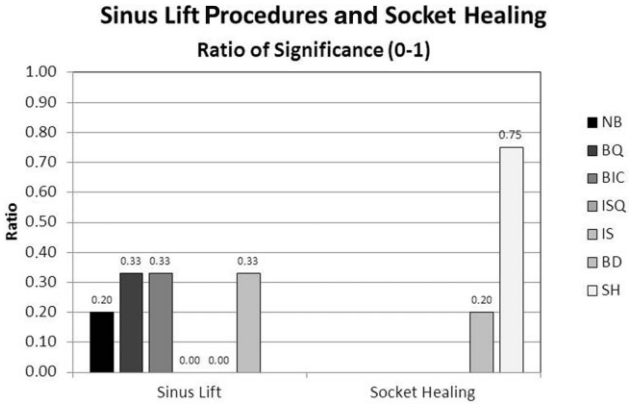

Figure 2 Ratio of significance for outcome variables of the use of PCs in sinus lift procedures and socket healing (NB: new bone formation; BQ: histologic bone quality; BIC: bone implant contact; ISQ: implant stability quotient; IS: implant survival; BD: radiologic bone density; SH soft tissue healing).

higher than the controls. Significant enhancement in radiologic density had been reported in 2/6 studies. Bone implant contact (BIC) (+13.0–127.7%) had been found to be significantly increased in 1/3 studies.[36,38,43] Implant stability (ISQ 1.0% higher than controls)[39,46] and clinical performance/implant survival (IS) (2.4% higher than controls)[32,36,38,39,47] had not been found to be enhanced by the use of PCs in any of the studies. Peri-implant bone height (+16.7% of control)[39] had been evaluated only in one study.

The resulting ratios of significance are shown in Figure 2 displaying only weak evidence for reliable enhancement of bone formation on the histologic/radiologic level and no evidence for improvement of implant stability/clinical performance/survival rate of implants placed into the grafted sinus floor.

General sources of bias for the use of PCs in sinus floor augmentation were the large variety of outcome parameters that had been assessed as well as the high variation in carriers/biomaterials used resulting in much smaller subsets of studies for the individual parameters than the number of included studies might suggest. More specific sources of bias in reporting in RCTs were that neither the mode of randomization nor the allocation concealment has been reported clearly in all studies. Other sources of bias were the use of historic controls[33,35] and the limitation of patients included into quantitative analysis.[34,47]

Socket Healing Procedures/Noncontrolled Studies. There were only 3 case reports[51–53] and two case series[54,55] available on the use of PRP[53–55] and PRF.[51,52] Only in one report,[55] synthetic, xenogenic and autogenous grafting materials were used as carriers. In this case oro-antral fistulas had been closed. No adverse effects and uneventful healing has been reported.

Socket Healing Procedures/Cohort Studies with Controls, RCTs. Eight RCTs and two cohort study with controls[56–65] were available for analysis. Two studies had to be excluded because nonmatching controls prevented the isolated assessment of the effect of PCs.[56,60] From the remaining 8 studies, 6 have used PRP and 2 have employed PRGF.[58,65] In all reports, PCs have been applied without carriers. Observation periods ranged from 1 week to 6 months. Most of the studies had applied scores to assess clinical and radiographic healing. Variations in description and quality of documentation between the individual reports, unfortunately, did not allow for direct comparison of numerical results. Well documented radiographic scores that differed significantly in favor of PRP were found only in 1/5 studies, soft tissue scores were significantly better than controls in 3/4 studies (Figure 2). One study had reported a significantly reduced rate of alveolar osteitis.[65] Three studies had also assessed a VAS based pain score with significant differences in favor of the use of PCs.[57,58,65]

Again, a potential source of bias in terms of the PRISMA criteria has been the incomplete reporting of randomization procedures and blinding of examiners and/or patients. The reporting of results on pain scores may also be subject to bias as appropriate double blinded placebo procedures, which are considered standard in pain research, were not clearly described or not applied.

Lateral/Vertical Augmentations. The use of PRP in conjunction with augmentations of the alveolar crest has been described in 7 case reports,[66–72] three case series[73–75] and two RCTs.[76,77] Autogenous bone ($n = 6$), mesenchymal cells ($n = 4$) and xenogenic/synthetic materials ($n = 3$) had been used as grafting materials. While non-controlled studies reported favorable results, controlled trials using autogenous bone grafts have described no benefit with respect to soft tissue healing, bone resorption and implant stability.[76] The use of PRP in conjunction with bovine bone mineral and titanium mesh has been reported to be associated with a significantly reduced rate of soft tissue complications with mesh exposure, however, without effect on clinical performance of the implants placed later on.[77]

The small number of controlled studies precludes a useful analysis of potential sources of bias in reporting as the lack of objective comparison with appropriate controls is the major limitation for evidence in the use of PCs in lateral/vertical augmentations.

Periodontal Applications

Overall comparison of results was impaired in a considerable number of studies by the fact that controls were not clearly designed to assess the effect of the growth factor rather than the effect of a carrier or the effect of a growth factor/carrier combination compared to established treatment modalities such as open flap debridement. Reports were therefore considered separately

TABLE 3A Studies on the Use of Platelet Concentrates (PCs) in Intrabony Pockets (Weighted Means and % of Controls)

	PCs without Carriers vs. OFD		PCs vs. PCs with Carriers		PCs with Carriers vs. Carrier Alone		PCs with and without Carriers cs. GTR	
	mm	% Contr.	mm	% Contr.	mm	% Contr.	mm	% Contr.
PD red.	1.26	36.0	0.70	30.0	0.81	23.8	0.3	5.8
CAL gain	0.68	20.7	1.24	63.6	1.14	59.9	0.2	9.2
LBF incr.	2.01		1.35	127.0	0.53	16.2		
GM incr.	0.40	114.6	0.09	25.9	0.12	8.6	0.1	5.5

PD: Pocket depth reduction; CAL: Gain in clinical attachment level; LBF: Linear bone fill; GM: Gingival margin level.

according to the individual setups. Some reports had to be excluded at this level because there was at least one additional component such as a second carrier material, additional biomaterial use or additional use of cells in one group that confounded the analysis.[78–80] Moreover, studies that compared different plasma fractions or assessed the effect of patient factors (e.g., smoking) on the efficacy of PRP were not considered.[81–83] Follow-up times in periodontal indications were mostly 6 and 12 months with a min. of 4.5 and a max. of 18 months.

If carriers were used for application of PCs, a variety of materials has been employed ranging from synthetic tri-calcium phosphate (TCP) and hydroxylapatite (HA) to bovine bone mineral, algae skeletons and demineralized freeze-dried bone allograft (DFDBA). The large number of different preparations made a direct comparison among individual materials impossible.

Periodontal Applications/Noncontrolled Studies. Seven case reports,[84–90] one case series[91] and three cohort studies without controls[92–94] have been identified, that reported on application of PRP for the treatment of intrabony pockets or recession treatment.[84] A large variety of carriers has been used with no preference to any material. One study[94] had used no carriers at all. On average, 16 patients had been evaluated in the studies of the latter two categories with a follow up between 12 and 24 months. No adverse reactions or coagulation disorders have been reported. Results of both soft tissue and bone tissue have been judged favorably in all studies.

Intrabony Pockets/Cohort Studies with Controls, RCTs

PCs without Carrier vs. Open Flap Debridement (OFD). Four RCTs were available for evaluation. One of them had evaluated both PRP and PRF,[95] which were considered separately, whereas the rest had used PRF only.[96–98] The overall number of patients included in controlled trials was 189. Differences in weighted means of evaluated parameters are displayed in Table 3A. CAL, PD, BF were found to be significantly enhanced by the use PRP or PRF alone in 4/5 evaluations, while the GM level has been found significantly improved in 3/5 analyses.

PCs vs. PCs and Carrier. Two cohort studies with controls[99,100] and 4 RCTs[96,101–103] could be evaluated. Two RCTs had used PRF, the remaining reports had tested PRP. The number of patients included had been 147. Table 3A shows the differences in weighted means and percentage of controls. Significant differences were reported for PD and CAL in 3/6 reports, LBF in 4/6 reports. Changes in the level of the gingival margin (GM) have reached significance in 0/4 evaluations.

PCs and Carrier vs. Carrier Alone. Thirteen RCTs on the use of PCs in conjunction with carriers were

TABLE 3B Studies on the Use of Platelet Concentrates in Recession Treatment and Furcation Treatment (Weighted Means and % of Controls)

	Recession Treatment		Furcation Treatment	
	mm	% Contr.	mm	% Contr.
PD red.	0.06	1.5	1.42	52.0
CAL gain	–0.03	–2.4	1.67	139.3
LBF incr.	NA	NA	1.20	
GM incr.	0.15	20.6	0.17	34.9
TkT	–0.02	–21.5	NA	NA
WkT	0.41	3,6	NA	NA

PD: Pocket depth reduction; CAL: Gain in clinical attachment level; LBF: Linear bone fill; GM: Gingival margin level, TkT: Thickness of keratinized tissue; WkT: Width of keratinized tissue, NA: not applicable.

included into the evaluation.[104–116] Only PRP has been used in these studies. A total number of 379 patients had been included into these studies. Differences in the parameters assessed are can be seen in Table 3A. PD and CAL were found to be significantly improved in 8/13 reports, LBF had been found to be significantly increased in groups with PRP only in 3/10 studies and the GM was significantly affected in 0/5 studies.

PCs with/without Carriers vs. GTR. Eight RCTs[117–124] were analysed in this group. All of the studies had evaluated PRP. Six studies had a combination of a carrier and a barrier membrane in conjunction with PRP tested against this combination alone. One study had evaluated a PRP/carrier/membrane combination against the membrane alone[121] or open flap debridement only.[124] As the latter studies did not allow for the isolated assessment of the use of PRP they were excluded from the evaluation. The six studies with comparable setups had included 141 patients. Differences in PD reduction, CAL gain, LBF and GM level are shown in Table 3A. None of these parameters was found to be significantly different in 6/6 studies.

A comprehensive overview on the ratios of significance on the four outcome variables in different test scenarios in the treatment of intrabony pockets is given in Figure 3.

Recession Treatment/Cohort Studies with Controls, RCTs

Two cohort studies with controls[125,126] and six RCTs[127–131] were available for analysis. One of them had to be excluded because of comparison with a different growth factor preparation without additional controls.[128] Observation times ranged from 3 to 12 months. From the remaining six studies under evaluation, three had used PRP, two used PRF and one had used PRGF. PD reduction and CAL gain were 0.06 mm (1.5%) and –0.03 mm (2.4%) lower than in the controls. Differences in GM level, tissue thickness (TkT) and width of keratinized tissues (WkT) were 0.15 mm (20.6%), –0.02 mm (21.5%) and 0.41 mm (3.6%), respectively (Table 3B). With the exception of one report[132] showing a significant reduction in PD after 8 months, none of the studies had been able to show significant differences in the test groups vs. controls for any of these parameters, (Figure 4).

Furcation Treatment/Cohort Studies with Controls, RCTs

Only three RCTs could be evaluated, one using PRP in conjunction with bovine bone mineral[133,134] and one using PRF without a carrier.[135] Sixty-four patients had been included into these trials. PD reduction and CAL gain were higher in the growth factor groups by 1.42 mm (52.0%) and 1.67 mm (139.3%), respectively. Change in LBF was 1.20 mm greater and GM level was

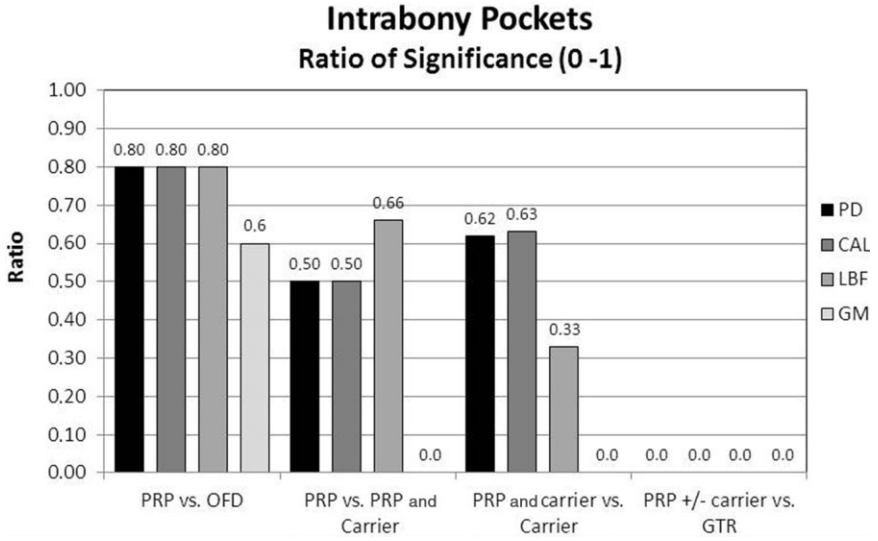

Figure 3 Ratio of significance for outcome variables of the use of PCs in the treatment of intrabony pockets (PD: probing depth; CAL: clinical attachment level; LBF: linear bone fill; GM: level of the gingival margin).

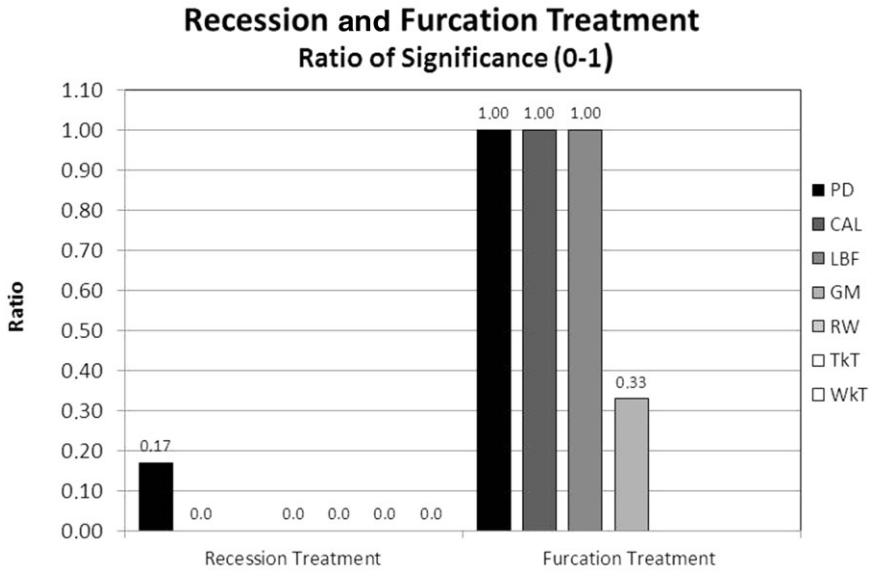

Figure 4 Ratio of significance for outcome variables of the use of PCs in recession and furcation treatment (PD: probing depth; CAL: clinical attachment level; LBF: linear bone fill; GM: level of the gingival margin/recession depth; RW recession width; TkT: thickness of keratinized tissue; WkT: width of keratinized tissue).

0.17 mm (34.9%) higher than in the controls. PD, CAL and LBF were found to be significantly improved in all three studies; the difference in GM level was significant only in one report[135] (Figure 4).

A common source of potential bias in the sense of the PRISMA criteria in almost all studies has been the scarce description of the randomization procedure that also impaired identification of proper allocation concealments. Another source of bias in interpretation of the results has been the fact that both the variation in experimental setups (i.e., the design of appropriate control groups) and the use of a large variety of carrier materials have contributed to the heterogeneity of the studies under analysis.

Other Indications

Endodontic treatment has been combined with the use of PRP,[136–142] PRF[143,144] and PRGF[145] in 7 case reports and three controlled studies.[137,139,141] All studies reported favorable and positive results with respect to periapical regeneration, pulp tissue regeneration, apical closure or regain of vitality. RCTs are required to consolidate this first positive impression of this area of application of PCs.

PRP has also been used to enhance osseointegration and implant stability in three cohort studies with controls.[146–148] None of these studies has shown a benefit for implant stability through the use of PRP.

The use of PRP and PRGF[149,150] in *bisphosphonate related osteonecrosis of the jaws (BRONJ) or osteoradionecrosis (ORN)* has shown to be a quite recent area of application and has been reported in 2011 and 2012 in three cohort studies without controls[149–151] and three controlled studies.[152–154] While the case series reported favorable results, the controlled studies were either negative[154] or they were difficult to interpret due to simultaneous use of low level laser therapy.[153] Thus, current evidence does not support the use of PRP in conjunction with BRONJ or ORN.

The remaining indications have been evaluated in too few studies[155–166] (see Table 2) to assess the effect of the use of PCs in these applications on a reliable basis mostly due to either lack of controlled studies or due to ambivalent results.

Human Recombinant Growth Factors

Eighty-one reports on the use of human recombinant growth factors could be identified. Among the many different signals available for enhancement of tissue repair, only rhPDGFs and rhBMPs have been explored in a quantitatively meaningful manner in the oral and maxillofacial area yet. Among the three isoforms of PDGFs, only rhPDGF-BB has been reported and from the more than 30 members of the BMP family the use of rhBMP-2, rhBMP-7 and rhGDF-5 (Growth and Differentiation Factor 5) have been described.

The majority of reports have been noncontrolled studies ($n = 46$) with 17 case reports, and 29 case series and cohort studies without controls. Twenty-nine controlled studies with 8 cohort studies with controls and 21 RCTs were available as well as 6 reviews (Table 4).

Platelet Derived Growth Factor-BB (PDGF-BB). Thirty papers on the use of rhPDGF-BB have been included. Among these reports, the use in periodontal applications has been most frequently described ($n = 15$). Other indications were focused on implant site development, that is, socket healing ($n = 3$), sinus floor augmentation ($n = 2$) and augmentation of the alveolar crest ($n = 6$).

Periodontal Applications/Noncontrolled Studies

Seven of the papers on the use of rhPDGF-BB in periodontal therapy were case reports or noncontrolled dose finding studies in intrabony pocket treatment,[167–169] recession treatment[170,171] and furcation treatment.[172,173] The dosages employed ranged between 300 µg/ml and 5000 µg/ml. The carrier used for the growth factor had been βTCP in five of the six papers; one study had used DFDBA (169) and one had employed an acellular dermal matrix allograft (ADM).[173] Binding of the growth factor to the carrier surface had been achieved by adsorption through soaking of the carrier in the PDGF solution. Application of both the lower and the higher dosage levels had been followed by satisfactory periodontal regeneration. No adverse effects had been reported.

Intrabony Pockets/Cohort Studies with Controls, RCTs

Four RCTs[174–177] and one controlled study[178] had evaluated rhPDGF-BB in the treatment of intrabony pockets. Two studies[174,175] had assessed direct comparison of 300 mg and 1000 mg/ml, respectively, with controls after 3 and 6 months. One of these studies reported significant enhancement of LBF after 3 and 6 months but only temporary enhancement of CAL and GM level (recession depth) in the lower dosage group after 3 months,[175] whereas the second study[177] found significant enhancement for CAL gain and PD also after 6 months. The third study[174] reported a 36 mo. follow-up on the patients from the previous paper.[175] Unfortunately, a longitudinal comparison of variables was omitted in favor of the definition of benchmarks and a percentage of successful treatments.

A very early study by Howell and coworkers[176] had used a combination of rhPDGF and insulin-like growth factor-1 (IGF-1), a growth factor that promotes mesenchymal proliferation, in two dosages (50 µg/ml and

TABLE 4 Studies on Recombinant Growth Factors According to Level of Evidence and Indication

		Case Reports Case Series Cohort Studies without Controls				Cohort Studies w Controls RCTs				Systematic Reviews, Meta-Analyses
Indication		PDGF	FGF	EGF	BMPs	PDGF	FGF	EGF	BMPs	
Periodontology	Intrabony pockets	167–169			235	174–178	240,241		234,236	246,256
	Recession	170,171				179–181				
	Furcation	172,173								
Sinus floor augmen.		184,185			196,198,199				203–205,207,211,212	
Socket healing		182,183				192			202,208,209	
Lat. / vert. augm.		185–191			195,197,200,201				206,210	
Segmental reconstruction					213–223					224,225
CLP		194			226–228				229–231	232,233
Epithelial regeneration		193		245				242–244		
BRONJ / ONR					239					
Distraction osteogenesis					238					
Craniofacial defects					237					

150 µg/ml) and thus did not allow for evaluation of rhPDGF-BB alone. The controlled study[178] had compared three dosage levels (500 µg, 1000 µg and 1500 µg/ml), with DFDBA as carrier, however, the growth factor free controls had received a different biomaterial (bovine bine mineral) and a collagen membrane. Thus, no conclusion was possible on the efficacy of the growth factor alone. Both studies, therefore, had to be excluded from the comprehensive consisderation. In summary, in the three studies that had tested rhPDGF-BB in a manner that allowed for isolated assessment of the growth factor effect, CAL had been found to be significantly improved in 2/3 studies whereas LBF had been significantly enhanced in all 3 RCTs (Figure 5).

Recession Treatment/Cohort Studies with Controls, RCTs

Two RCTs[179,180] and one controlled study[181] had assessed the effect of rhPDGF-BB in conjunction TCP on the treatment of gingival recessions vs. a connective tissue graft. No significant clinical benefit (PD,GM) could be detected in the RCTs (Figure 5); however, histologic evaluation had shown the formation of Sharpey fibres after the application of rhPDGF-BB in contrast to the controls.[181]

A potential bias in the interpretation of results of the use of rhPDGF in periodontal regeneration may arise from a lack of matching controls,[178] the use of additional growth factors[176] and to some degree from over-reporting through a follow up study on the same patient population.[174,175] Moreover, only one study[177] had completely reported the randomization procedure and allocation concealment.

Implant Site Development

Applications of rhPDGF-BB for implant site development such as socket healing,[182,183] sinus floor augmentations[184,185] or augmentations of the alveolar crest[185–191]) have been communicated almost exclusively through case reports or case series. All papers have reported good healing without any adverse events. In one controlled series[188] rhPDGF had been used in conjunction with three biomaterials, however, without controls using biomaterials only, which precluded isolated evaluation of the growth factor effect. Only one controlled study[192] had looked at histologic results of socket healing in 15 patients, but could not find a significantly increased rate of bone formation in sockets with application of rhPDGF-BB despite a trend for enhanced bone formation.

Other indications such as soft tissue healing[193] or repair of alveolar clefts[194] have been only reported anecdotally in just one paper each. They are therefore not considered further in this analysis.

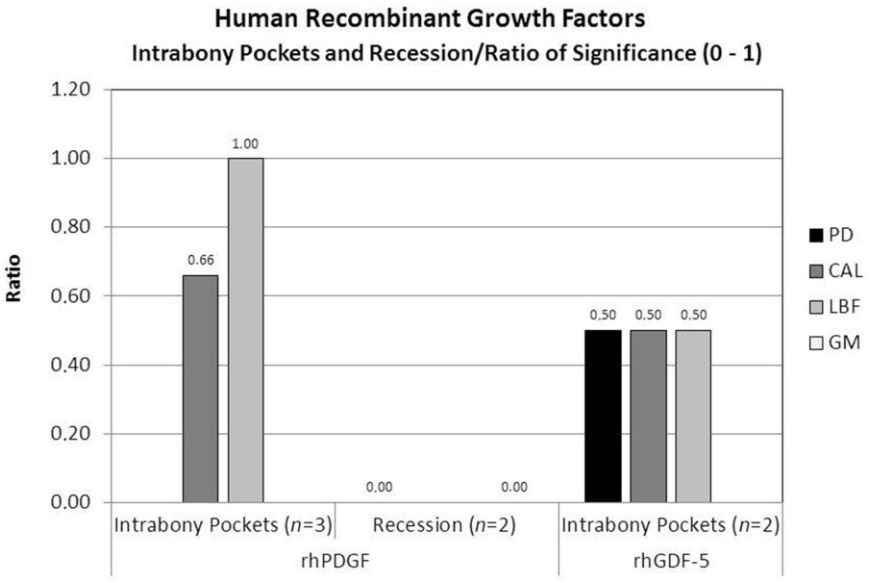

Figure 5 Ratio of significance for outcome variables of the use of human recombinant growth factors in the treatment of intrabony pockets and recessions (PD: probing depth; CAL: clinical attachment level; LBF: linear bone fill; GM: level of the gingival margin).

Bone Morphogenic Proteins (BMP-2, BMP-7, GDF-5). The number of studies on the use of bone morphogenic proteins has been the second largest in this evaluation with 47 papers. Eleven different clinical indications have been reported, the techniques of implant site development ($n = 15$) being the most frequent followed by repair of segmental defects of the mandible ($n = 13$) and alveolar cleft repair ($n = 8$) (Table 4).

Implant Site Development/Noncontrolled Studies

Two case reports[195,196] and five noncontrolled studies[197–201] have been identified, that reported on sinus floor augmentation,[196,198,199] and on socket healing and augmentation.[195,197,200,201]

The case reports have used allogenic material[196] and collagen as carrier;[195] the latter describing a rather large post resection defect repair in which a titanium mesh had been used to stabilize the graft volume.[195] The four dose finding studies had employed only collagen. The dosages applied ranged between 120–440 μg,[200,201] 1500 μg[198] and 1770–3440 μg (up to 8 ml of 430 μg/ml[199]). The metric vertical changes had been reported to range between 15.7 and 2.3 mm in sinus lift augmentations[199] and 10,4 mm in socket healing applications,[200] whereas the increase in bone width and bone height in augmentations of the alveolar crest had been only 0.2–0.4 mm and 0,2 to 0.8 mm, respectively.[200,201] No serious side effects were reported, however, oedema as well as prolonged erythema and swelling had been registered in a substantial number of cases.[199,201]

Implant Site Development/Cohort Studies with Controls, RCTs

Three cohort studies with controls[202–204] were available for analysis, two of them on the same patient population.[203,204] One study[202] had to be excluded from the evaluation, because control sites had received different carriers than the sites with rhBMP. Six RCTs[205–210] have been identified, that evaluated the use of rhBMP2 in socket healing,[208,209] sinus floor augmentation[205,207] and on lateral augmentations.[206,210] The latter two of these studies had evaluated the same cohort with a five year observation period in between and had used bovine bone mineral as carrier, while the rest of the studies had employed collagen sponges. Loading of the carrier with the growth factor was accomplished by soaking the biomaterial with the respective rhBMP solution. Dose levels per ml ranged between 500 μg,[206] 750 μg,[207,208] 833 μg[203,204] and 1500 μg.[207,208] The absolute amounts administered were quite variable, depending on the volume of the carrier and of the corresponding volume of the growth factor solution, ranging from 2500 μg[203,204] to 5200–24 000 μg[205,207] in sinus lift studies and 500 μg in lateral augmentations.[206,210] Moreover, two RCTs have assessed the effect of rhGDF-5 in sinus lift procedures.[211,212] They have used βTCP as carrier and as controls in conjunction with autogenous bone in contralateral sinuses. 500 μg GDF-5/g TCP had been used with the TCP particles pre-coated with the lyophilized growth factor.

The *sinus lift* studies with the low dose of rhBMP-7[203,204] had reported only one out of three patients with sufficient bone regeneration to place implants. The remaining two studies with higher amounts of rhBMP2[205,207] had shown levels of regenerated bone that compared favorably to the control sides where autogenous bone had been placed height (–0.4 mm/–4.3% of the controls). Bone width was by 2.8 mm (62.2%) smaller than the controls; histologic bone density had been 55.4% lower than the controls. The implants placed in the regenerated bone showed no significant difference in survival rate compared to controls. The studies using GDF-5 had reported no significant differences in bone formation on the histologic level nor in gain in bone height in augmentations with growth factor vs. controls with autogenous bone.[211,212]

The use of rhBMP-2 had been evaluated in *socket healing* in one RCT with nontreated sockets and sockets with collagen carrier only as controls.[208] Significant enhancement of bone regeneration in both height and width has been reliably achieved with a concentration 1500 μg/ml but did not occur with 750 μg/ml.

There was only one group of patients that had been evaluated in two follow-up studies for the use of rhBMP2 in *lateral augmentations*. The initial study[210] had used 500 μg of the growth factor in conjunction with bovine bone mineral and has not found significantly increased bone formation but an enhanced maturation to lamellar bone. The follow-up study 4.5 years later[206] has not been able to show any clinical advantage of the use of rhBMP2 over the application of the carrier without growth factor.

Adverse effects registered in all implant site development applications were identical to those already

reported in the dose finding studies with oral odema and oral erythema being the leading complaints.

A potential source of bias in the reporting of the use of BMPs in implant site development has been again the frequently scarce description of randomization procedures. Moreover, there is a tendency for over reporting with two populations being reported twice.[203,204,206,210]

Segmental Reconstruction of the Mandible

No RCTs have been identified for the use of BMPs in segmental reconstructions of the mandible. Six case reports,[213–218] five case series[219–223] and two reviews[224,225] were available for analysis. There were two case reports that had used a protocol that was entirely different from the rest of the studies using BMPs for segmental reconstruction of the mandible. One case report[214] had used distraction osteogenesis before implantation of the collagen carrier and rhBMP-2 and one report had used two coralline hydroxylapatite blocks infused with rhBMP-7 precultivated in the Pectoralis Major muscle for vascularized mandibular segmental reconstruction.[215] These two studies were not further considered in the analysis. Apart from these two reports, a total number of 39 segmental reconstructions have been reported using rhBMP2[213,217–222,224] and rhBMP7.[223] The dosages employed had been between 4200 and 24000 µg. The length of the segmental defects treated had been between 3 and 9 cm. Mandibles had been stabilized using reconstruction plates during bone formation originating from the implanted growth factor carriers. One study had used additional allogenic bone trays along with the reconstruction plates.[213] Collagen sponges had been used as carriers for rhBMP-2, whereas demineralized bone matrix in conjunction with poloxamer, an amphiphilic polymer, had been used as carrier for rhBMP-7. Additional autogenous cancellous grafts from the iliac crest[218] and allogenic bone chips[219,222] as well as centrifuged aspirated bone marrow stroma cells[217] have been used in three studies (8 patients). 35 repairs had been performed as primary reconstructions after resection of benign pathology of the mandible including cysts,[219] trauma,[19] benign neoplastic diseases[213,217–223] and sequelae of chronic infections.[219,221,223] Four reconstructions had been done in a secondary approach after the intermediate use of bridging plates. Thirty-four (87.2%) reconstructions have successfully healed and restored mandibular continuity. Four of the five failures had occurred in secondary reconstruction cases.

Cleft Repair

Three case series[226–228] and three cohort studies with controls[229–231] as well as two reviews[232,233] have been identified for the use of BMPs in cleft repair. The dosages applied ranged between 3200 and 4200 µg soak-loaded on a collagen fleece. Only rhBMP-2 has been applied. Control groups had received either periosteoplasty[229] and/or iliac crest grafts.[229–231] All papers reported successful bone formation in the patients having received rhBMP-2. The bone volume induced by rhBMP-2 in the cleft defects was quite variable and amounted to approximately 71.7% to 94.6%[231] of the initial defect volume. Controlled studies reported variable amounts of induced bone in comparison to iliac crest grafts ranging from −16.5%[230] to +65.6%[231] of the bone graft volume. The reviews confirmed these results albeit with some formal criticism on study procedures and concluded that more and larger high power RCTs are required before definite conclusions can be drawn on the use of BMPs in alveolar cleft repair.

Potential sources of bias in the randomized controlled studies on rhBMPs in alveolar cleft repair are incomplete descriptions of random sequence generation, allocation concealment and blinding performance.[232] Moreover, very variable defect volumes may tend to overestimate the potential of rhBMPs for bone repair when small defects are included.

Other clinical applications for BMPs have been reported for periodontal repair,[234–236] craniofacial defects,[237] distraction osteogenesis in Pierre-Robin cases[238] and bisphosphonate related necrosis of the jaws (BRONJ).[239] Only periodontal repair has been evaluated in two RCTs using 500 µg of GDF-5 /g TCP in the treatment of intrabony pockets. One of them reported significantly reduced PD and enhanced CAL and bone fill[234] compared to open flap debridement while the other study had been unable to find significant changes[236] (Figure 5). The remaining indications are too scarcely reported and analysed yet to allow for a useful evaluation.

Other Growth Factors (bFGF, KGF, EGF). Apart from PDGF and BMPs, there were three other growth factors that have been used for tissue repair in the OMF area. Two sequential RCTs have assessed the effect of 0.3 to 4 mg/ml bFGF on periodontal regeneration.[240,241] The earlier study[240] that had used 0,3 to 3 mg/ml has been able to show increased bone height only in the high dose

group but no enhancement of CAL gain. The later report[241] had confirmed this effect with significant gain in bone fill and no significant gain in CAL gain.

Three RCTs[242–244] have evaluated the effect of human recombinant keratinocyte growth factor (rhKGF) as preventive agent for severe oral mucositis during high dose chemotherapy. Using an intravenous administration of 60–180 μg/ kg body weight, a significant reduction in the occurrence of high grade mucositis was observed.

Finally, topical administration of human recombinant epithelial growth factor (EGF) using mouthwash in an RCT has suggested a prophylactic role of EGF in reducing the severity and delaying the onset or oral ulcerations during cancer chemotherapy.[245] However, due to the small sample size, no statistical evaluation had been performed.

The rare use and the low numbers of studies on the use of FGF, KGF and EGF suggest that these three growth factors are unlikely to play a substantial role in the near future.

DISCUSSION

This systematic review of the clinical use of growth factors for the enhancement of tissue repair has identified 19 different clinical situations in which growth factors have been used to augment tissue regeneration. There is a certain degree of overlap between clinical indications in which autogenous growth factors from PCs and human recombinant growth factor have been used. The results have shown that case reports, case series or noncontrolled studies still make up a significant number of reports in this field. This portion has been quite variable with a high number of RCTs and controlled studies on the use of PCs in periodontal indications vs. a high number of case reports and series in the application of BMPs in segmental mandibular reconstruction.

The application of autogenous growth factors using PCs has shown to be well documented by RCTs in periodontal indications. The use of PCs alone vs. open flap debridement in the treatment of intrabony pockets has shown a high to moderate degree of significance for improvement in all four outcome variables (PD, CAL, LBF, GM) (Figure 2). When applied in conjunction with a carrier, further improvements compared to the use of PCs alone were registered with a moderate degree of significance. When compared to the use of carriers only, LBF and GM showed improvements only at a low level of significance, indicating that the scaffolding effect of the carrier alone may already be a major contributing factor for bone tissue regeneration and that the scaffold at the same time may act as mechanical support for the level of the gingival margin. Interestingly, no significant improvements could be achieved by the additional use of barrier membranes, suggesting that contribution of the overlying tissue to regeneration in the defect is necessary to respond to the regenerative signals of the PCs.

Data on other periodontal indications such as recession treatment appear to indicate almost unanimously that PCs do not provide any advantage in the treatment of gingival recessions whereas data on furcation treatments suggest that repair may be significantly enhanced; however, as complete closure of the furcation area is not achieved, the clinical value of this effect is considered to be doubtful.[133]

The results of this review are partially in line with previous reviews on the use of PCs in periodontal indications[11,246,247] and add new evidence to the pattern of results reported there. The results of that paper have been challenged in a recent discussion[248] pointing out several short comings and drawbacks[249] of the studies that had been evaluated in the review and that are considered in the present report, too. It is true, that standardization with respect to patient factors, defect geometry and other variables such as grafting material is of great importance for the validity of the conclusions drawn from the evaluation of studies in a systematic review. However, here the limits of evidenced based approaches become visible. Systematic testing of a population characterized by as few as five variables with only dichotomic manifestation would already require hundreds of patients for an RCT. While this would surely be perfect in an ideal world, the accumulation of individual RCTs with slightly different setups and different foci may nevertheless generate knowledge that gives some guidance for good clinical practice and at the same time reflects the changing setting of variables in daily clinical work. Having said this, it should be kept in mind that the results derived from these studies are merely short term results that make estimation of long term effects difficult.

The use of PCs in sinus floor augmentations has not produced data that could provide convincing evidence that the addition of PCs to grafting materials is beneficial with respect to treatment outcome. There are

indications for improvement of early bone formation or bone implant contact on the histologic level; however, no significant advantage with respect to implant stability or implant survival has been shown. These results are in accordance with previous systematic reviews that concluded that the use of PRP may be beneficial for bone formation[250] but is not relevant for clinical outcome parameters.[250–254]

Socket healing has been identified as a rather new area of application that has provided also a relatively high number of controlled studies. Unfortunately, high variability in the definition and assessment of outcome parameters has limited a comprehensive evaluation. So far, there is little evidence that the use of PCs may enhance bone formation during socket healing but the potential to improve the healing of overlying soft tissues appears to be larger. Nevertheless, at the moment evidence is only weak or ambivalent that PCs are beneficial for socket healing.

A frequently applied criticism is the incomplete reporting of randomization procedures and of blinding of patients/examiners. While this weakness has to be mentioned to caution readers about possible sources of bias, the majority of RCTs that have generated objective metric data are hardly likely to be affected by substantial bias if a reasonable standard of allocation concealment has been maintained. A recent report[255] has shown that overestimation of intervention effects is only minor (1–3%) in cases of unclear sequence generation or allocation concealment if objective outcome data are generated. In contrast, studies that have evaluated subjective scores (e.g., pain) in setups that are difficult to comply with placebo controlled approaches may be subject to considerable degree of bias.[255] This may be particularly difficult in studies on socket healing with sockets filled or not filled with PRP gel or PRF after tooth extraction, it may be difficult to completely blind the patient to the treatment allocation if nothing is filled into the control socket.

The use of recombinant growth factors is currently strongly focused on PDGF and BMPs. From the three isoforms of PDGF only rhPDGF-BB has been evaluated yet. From the more than 30 proteins from the BMP group, rhBMP-2 appears to be by far the most frequently used factor while rhBMP-7 and rhGF-5 seem to play only a minor role: Although other growth factors such as bFGF have also been used with some success in periodontal repair, the clinical application of this factor appears to be very limited. The same applies to epithelial and keratinocyte growth factors which may be of some value in prevention of severe mucositis during multimodal oncologic therapy regimens, but applications outside of this area have not yet been reported.

The use of rhPDGF-BB has been focused on periodontal regeneration. Here, linear bone fill had been reliably achieved whereas significant permanent increase in clinical attachment level has only been reported in two of three studies. Treatment of gingival recession has not been significantly improved by the application of rhPDGF-BB. This is in line with previous reviews.[256] Hence, present data appear to suggest that the efficacy of rhPDGF-BB in periodontal regeneration has a stronger tendency for enhancement of bone regeneration but otherwise is not much different from the use of autogenous PCs, which are available at much lower costs. However, to validate this assumption, RCTs will be necessary for direct comparison. The application of rhPDGF-BB in implant site development using socket fill, sinus floor augmentation and lateral or vertical augmentation of the alveolar crest is currently not supported by evidence for enhancement of bone formation.

This has been reported to be different for the use of bone morphogenic proteins. However, the successful application appears to be site specific depending on the carrier used in the respective situations. In mechanically protected sites such as sinus floor augmentations and socket repair, bone regeneration appeared to have worked well after implantation of a collagen carrier with rhBMP-2, whereas the gain in width or height in lateral or vertical augmentations had been unsatisfactory when this carrier had been used. If a mechanically more resistant osteoconductive carrier had been employed, an enhancing effect on the quantity of bone formation and on volume stability around dental implants during medium term follow-up did not occur.[206,210] However, in these studies, rhBMP-2 and bovine bone mineral had been used in conjunction with collagen membranes in a GBR approach. Like with the use of PCs in periodontal regeneration, the effect of the applied growth factor may be reduced when the overlying soft tissue is shielded against the defect by barrier membranes. With the current biomaterials available as carriers or fillers, the role of rhBMPs in the augmentation of smaller to medium sized dentoalveolar defects remains unclear. Space-making osteoconductive carriers may not require substantial enhancement of bone formation in many

periimplant defects during simultaneous grafting and implant placement, when used in conjunction with barrier membranes. Collagen carriers can only be used in mechanically nonchallenging situations or require the use of mechanical protectors such as titanium meshes, which have to be removed later on requiring wide exposure and subsequent resorption of the newly generated bone. More RCTs will be necessary to specify the advantages and limits of the use of rhBMPs in dentoalveolar augmentation.

In larger defects, the application of BMPs appears to be quite effective. A success rate of 87.2% in primary reconstructions of mandibular continuity after ablative surgery for benign bone pathologies as well as up to 94.6% volume fill of alveolar cleft defects is an acceptable result. The long term results with respect to volume maintenance and implantatability of the reconstructed bone for occlusal rehabilitation remain to be determined, as only 5 of the 39 reported mandibular reconstructions had undergone implant placement.[224]

Moreover, it should be kept in mind that 4 of the 5 reported failures in reconstruction have occurred in secondary reconstruction cases, indicating that preservation of the periosteum in immediate reconstruction cases after subperiosteal resection of benign pathology may be a crucial factor for successful use of BMPs in mandibular segmental reconstruction. Nevertheless, the results presented in the currently available studies indicate considerable potential for successful applications in selected cases.

The side effects of the use BMPs in particular have been reported to be long lasting edema formation that is more pronounced than the swelling following reconstruction with autogenous bone,[213] as well as erythema in the vicinity of the site of implantation. Although no severe adverse events have been reported for the use in the OMF area, the occurrence of oedema has caused dysfunction after the use of BMPS for spinal fusion with subsequent dysphagia.[257] Excessive swelling due to oedema formation may be attributable to the administration of gross overdoses of BMPs in mg scales compared to the naturally occurring level of BMPs in native bone which has been reported to be around 6–7 ng/g bone matrix. Another biological side effect of the use of human recombinant BMPs is the induction of antibodies against these growth factors,[204,207,212] which may not only jeopardize future use of BMPs in these individuals but also may be associated with cross reactions against naturally occurring growth factors. Thus, the responsible clinical use of BMPs will require additional research in the development of more sophisticated carriers with biologically appropriate release characteristics of growth factors that allow for a dose reduction and a more controlled process of bone formation.

CONCLUSIONS

The use of autogenous growth factors in PCs has shown to be beneficial in the treatment of intrabony pockets at a reasonable level of evidence by reducing probing depth and by enhancing changes in clinical attachment level as well as linear bone fill within the limits of the observation periods. The application in conjunction with grafting materials has been superior to the use of PCs only or grafting materials alone. No benefits have been shown for the use of PCs in recession treatment. When used in furcation treatment, probing depth, clinical attachment level and linear bone fill improved significantly, however, without clinical benefit. No benefit for the final outcome could be shown for the use of PCs neither in sinus lift procedures nor in lateral/vertical crest augmentations.

The use of human recombinant growth factors is so far limited almost exclusively to rhPDGF-BB and rhBMPs (BMP-2, BMP-7 and GDF-5). The use of PDGF in the treatment of intrabony pockets has shown to reliably increase in linear bone fill but weaker evidence for permanent improvements of clinical attachment level. So far there is no evidence to support the use in recession treatment, sinus lift procedures, socket healing and lateral/vertical augmentations of the alveolar crest.

rhBMPs have shown to be effective in enhancing bone formation in socket healing (rhBMP-2) and sinus lift procedures (rhBMP-2 and GDF-5). No controlled studies are available for the use in mandibular segmental repair. Successful reports appear to be limited to primary reconstruction after ablative surgery for benign pathology with preservation of the periosteum.

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