

**ARE PHARMACEUTICAL COMPONENTS EFFECTIVE IN REPLACING BONE
AFTER INVASIVE PERIODONTAL SURGERY?**

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Abstract

Treatment of the diseased periodontium involves regenerating the structures that have been lost. This evidence-based report evaluates the effectiveness of pharmaceutical components in regenerating bone after invasive periodontal surgery. A methodical approach was used to locate a total of five relevant articles demonstrating the success of Demineralized Freeze Dried Bone Allograft (DFDBA), Polypeptide Growth Factors (PGF) and Enamel Matrix Derivatives (EMD). The DFDBA group showed greater bone fill and defect resolution than the control group. PGF was shown to be useful when co-administered as an adjunctive treatment to other osteoconductive materials. EMD was successful in reducing pocket depth, attachment loss and intrabony defects after a one year period. These three pharmaceutical components demonstrate great promise in their ability to regenerate bone after invasive periodontal surgery. However, future studies which are of greater duration, employ a greater population size, and are able to utilize a gold standard, must be conducted in order to provide consistent scientific evidence.

Introduction

Periodontal therapy focuses on halting the progression of periodontal disease and regenerating structures that have been lost around the teeth. This is difficult to achieve considering the complex nature of biological factors and biochemical events taking place in cells that allow for regeneration to occur. If left untreated, periodontal disease will undermine the supporting structures of the dentition, such as cementum, the periodontal ligament, and alveolar bone, collectively referred to as the periodontium, ultimately leading to tooth loss¹. Periodontal disease remains a serious problem, with a prevalence of 10-30% in the adult population, and can also affect people of younger ages depending on the type of periodontitis that is analyzed². However, many materials are available for use in periodontology that the practitioner can apply to help their patients to control this disease process.

This evidence-based report is aimed at evaluating the effectiveness of pharmaceutical components in regenerating bone after invasive periodontal surgery. In order to address this topic, each component of the question was defined to perform effective literature searches. Treatments involving any surgical procedure were considered to be invasive. Thus, the term invasive periodontal surgery was restricted to the conventional surgical technique called open flap debridement (OFP). Subsequent to surgery, a material is placed at the site of treatment that generates bone to fill the intraosseous defect. A pharmaceutical component was defined as any agent that is placed in the intrabony defect following surgery for the purpose of replacing bone. According to this definition, there are two main classes of pharmaceutical components that can be used for bone replacement and regeneration: osteoconductive materials, which serve as a scaffold for new bone formation; and osteoinductive materials, which actively stimulate the *de novo* synthesis of bone³. This report is limited to osteoinductive materials because of their

promising potential to also induce the formation of the periodontal attachment apparatus. In addition, osteoinductive materials were found to dominate the current literature for periodontal and bone regeneration⁴. An osteoinductive pharmaceutical component was considered to be effective if it was shown to have the potential for repair or regeneration, of bone or the entire periodontium. Repair refers to the process by which damaged tissues are substituted with a substance that may be similar or of lesser quality compared to the original tissue. On the other hand, regeneration occurs with the development of novel tissue that was lost in the disease process⁵.

Four osteoinductive materials were chosen to evaluate their potential in regenerating bone. These materials were Demineralized Freeze-Dried Bone Allografts, Polypeptide Growth Factors, Enamel Matrix Derivatives, and Bone Morphogenetic Proteins.

Demineralized Freeze-Dried Bone Allograft (DFDBA) involves freezing a tissue specimen and then dehydrating it at a low temperature in a high vacuum, resulting in its use as a bone grafting agent. DFDBA appears to have high osteogenic potential and may also contribute to partial periodontal regeneration. Controlled clinical studies have repeatedly demonstrated that using DFDBA in periodontal intraosseous defects results in significantly greater alveolar bone and probing attachment gain compared to open flap debridement alone⁶.

Polypeptide growth factors (PGFs) are a class of natural biological mediators that are able to regulate cell proliferation, chemotaxis, and differentiation during wound healing. Platelet derived growth factor (PDGF) and transforming growth factor - β (TGF- β) are growth factors that have been studied for periodontal regeneration and belong to the PGF family. A convenient and economic way to obtain high levels of PDGF and TGF- β was to use the platelet-rich plasma

technique⁷. The first human clinical trial of PDGF demonstrated significant improvement in intrabony defect fill after open flap debridement compared to the group that had surgery alone⁸.

Enamel Matrix Derivative (EMD), which is commercially available as Emdogain, demonstrates potential in periodontal regeneration. Emdogain consists of amelogenin and related proteins derived from porcine tooth buds dissolved in a vehicle solution called propylene glycol alginate. It is believed that amelogenins induce the formation of the periodontal attachment during tooth formation, thereby illustrating the application of EMD in invasive periodontal surgery². The fact that Emdogain is a porcine derived material may raise an ethical question about its use in humans. However, due to the similarity of EMD's among mammalian species, it is unlikely that an immune response will be mounted. A Cochrane review on EMD reports that it is effective as a regenerative material in invasive periodontal surgery².

Bone morphogenetic proteins are supported by a significant number of publications using a recombinant form of the agent in animal models. Despite the promising potential for this material, it was excluded from this literature review since it has not been tested in humans for the purpose of bone and periodontal regeneration⁹.

This evidence-based report will evaluate the effectiveness of DBA, PGF, and EMD in bone regeneration after invasive periodontal surgery.

Methods

A systematic approach was employed to identify potentially relevant articles demonstrating the effectiveness of the three pharmaceutical components of interest.

Search Strategy

The overall approach for DFDBA, PGF, and EMD was according to the following strategy. Three electronic databases were used to find articles with defined search terms for each respective material. The results from each search were narrowed down first by eliminating articles by title with respect to their relevance to the question being examined. Applying specific inclusion/exclusion criteria defined below allowed for elimination by abstract and article. In addition, all articles were readily accessible at the University of Toronto's Dental Library or via the University of Toronto Library's online journal subscriptions. Finally, articles that were determined to be relevant were critically appraised and assigned scores based on The Checklist to Assess Evidence of Efficacy of Therapy or Prevention¹⁰, referred to as the critical appraisal checklist in this report (see Table 1). The highest score that could be achieved was 17. A summary of articles eliminated after the critical appraisal stage are listed in Table 2.

Inclusion Criteria

The articles selected for this report had to meet the following specifications:

1. Articles had to be written in English.
2. Articles had to be published between January 1995 to January 2006.
3. Article had to use randomized control trials (RCT) as the study design.
4. Articles had to examine human subjects.
5. The outcomes of bone regeneration were measured and raw data were provided.

6. Studies were included if they also measured regeneration of the periodontal attachment apparatus.

Exclusion Criteria

1. The pharmaceutical component could not be defined as osteoconductive.
2. Articles had to include a control that involved surgery alone (Ex. open-flap debridement), without the pharmaceutical agent being examined.
3. More than one treatment modality could not be examined in the same study

Search Process

DFDBA

The searches for DFDBA articles were completed on PubMed using the MeSH Database. The studies searched were limited to January 1995 to January 2006. The following keywords were used: [MeSH(freeze drying OR freeze substitution) AND bone allograft] and [MeSH(freeze drying OR freeze substitution) AND bone regeneration]. From this search, 487 results were found, which were further eliminated by reducing the searches to include only those that were English, RCT studies, and human studies, yielding 189 studies. Then, 75 studies were eliminated by title and 105 studies were eliminated based on reading the abstracts. The final 9 studies were read, reviewed and criticized according to the checklist for the critical appraisal of literature and the inclusion and exclusion criteria. The resulting one acceptable study was then included in this report.

PGF

The search for PGF were performed on Ovid Medline (year 1996 to present). The first search which included the search terms: oral surgical procedures/or periodontium/or gingival/or periodontitis/or periodontal diseases/or alveolar bone loss/or periodontal surgery or periodontal

pocket yielded 27,932 articles. A second search containing the terms growth substances/or platelet derived growth factor/or platelet rich plasma had 307,982 articles related to it. Then, the first and second searches were combined (AND) to yield 1598 articles and the studies were further narrowed down to 61 articles by limiting to RCT only. Fifty-three articles were eliminated by title and based on reading the abstract, another 3 studies were eliminated. Finally, the 5 remaining articles were read and critically appraised, from which two relevant studies were selected.

EMD

Three electronic databases were used to find relevant articles about EMD. The first search was performed on Ovid Medline using the search terms: periodontitis, bone regeneration, periodontal diseases, alveolar bone loss, dental enamel proteins and emdogain. The search was limited to studies published between January 1995 to January 2006, yielding 37 articles. Twenty-nine articles were eliminated by title and reading the abstracts eliminated 3 studies. After reading the articles and assigning critical appraisal scores, 4 studies were eliminated, yielding one that was relevant.

The second search was done on PubMed between January 1995 to January 2006 with search terms: bone replacement AND periodontal disease, with a further selection of periodontal pocket using the MeSH database as the criteria. This resulted in 83 hits, which were further limited by restricting the search to RCT studies, English, and human studies, yielding 34 articles. Subsequently, 26 were rejected by title, 2 were rejected from abstracts and then 5 were rejected by reading and critically appraising the articles, yielding 1 relevant study. Lastly, a search was done on the Cochrane Library website to find review articles that have been published for EMD. Using Emdogain as a search term, 1 review article was found.

Results

An evidence table was constructed including each of the five relevant articles chosen for this report, following the critical appraisal checklist and classified according to the Canadian Task Force for Periodic Health Evaluations (CTFPHE) (reference the leake book as for the checklist). The study with the strongest study design and higher critical appraisal scores were listed first in Table 3. The amount of bone regeneration for each pharmaceutical component was assessed by examining the pocket depth (PD), clinical attachment loss (CAL), and intrabony defect depth (IBD). These variables were measured in each article chosen, and a reduction in these variables (defined in Table 4), was considered to represent bone regeneration. It should be noted that with bone regeneration, bone fill results in a CAL gain. The resultant data was used to compare baseline to endpoint of treatment in test and control groups. Graphs were constructed to identify trends (Figures 1-3) and raw data, which were provided by the articles, were grouped into Table 5.

The article by Masters¹¹ was a RCT, a strong design to assess effectiveness of therapy, resulting in Level I evidence and Grade A classification. The DFDBA group showed greater bone fill and defect resolution than the control group. However, the control group of open flap debridement had a greater PD, CAL, and IBD reduction than the DFDBA group. The treatment of DFDBA was not large enough to be statistically significant in any of the clinical parameters. Clinically, the control group had 0.74 mm of PD reduction and 0.87 mm reduction of CAL compared to the test group, suggesting that there is benefit from debridement alone and no appreciable influence from DFDBA. The results of this study are valid because the assignment of patients to treatment and control groups was randomized, loss to follow-up during the 12-month duration did not occur, and aside from the DFDBA intervention, the groups were treated

equally. Also, there was no significant difference at baseline between the groups ($p > 0.05$). However, the authors did not address the finding that the control was more beneficial than the DFDBA in their discussion. The critical appraisal score was 15, since the study was not double-blinded and the treatment effect was not large enough to be clinically important for PD and CAL.

Howell's⁸ study was a RCT with double-masked, paired design, allowing for Level I evidence and Grade A classification. In this study, high and low concentrations of recombinant human platelet derived growth factor - bb (rhPDGF-BB) and recombinant human insulin growth factor - I (rhIGF-I) were used to treat intrabony defects in periodontal patients. Lower concentrations of both materials did not yield statistically significant results, while higher concentrations caused significant increases in bony defect fills in both angular and furcation lesions ($p < 0.05$). However, there were no significant CAL gains in either of the test groups compared to control group and PD was not measured for angular lesions (Table 5). The safety of using this material in patients was also assessed and no adverse effects were found. A re-entry assessment for the lower concentration of growth factors was done at 6 months, which might not be long enough for the growth factors to show any effects. Therefore, they also made measurements of the high level groups at nine months, which demonstrated a 42% improvement in the bony defect fills compared to 19% in the control groups. Despite reporting percentages instead of absolute data, the study confirmed results from animal studies showing that growth factors are effective in improving bone regeneration after periodontal surgery.

Okuda '05⁷ also used a RCT with double-masked, paired design, allowing for Level I evidence and Grade A classification. They determined that Hydroxyapatite (HA) alone, or in combination with PRP, improved bone regeneration measured by PD and CAL, compared to the baseline values (Figures 1-3). The HA with PRP group demonstrated significant PD reduction

and CAL gains of 4.7mm and 3.4mm respectively, compared to 3.7mm and 2mm in the HA group (Table 5). Additional biological effects of PRP may explain these improvements. However, the IBD fills were not found to improve, nor was there a significant difference between the HA group and HA with PRP group. The results suggested growth factors could be used as an adjunctive treatment to commonly used osteoconductive materials.

The use of EMD as a pharmaceutical component has been investigated by Okuda '00¹² and Francetti¹³. Both studies are RCT's, which classifies them as Level I evidence and Grade A classification according to the CTFPHE. In addition, they are double blind, have clinical measurements recorded by a single examiner, and involve surgery done by a single operator and use customized bite blocks for reproducible x-rays, which contribute to the reliability of the studies. Impressively, both studies scored the highest possible score of 17 when evaluated by the checklist for critical appraisal. Both studies compare EMD to a control (open-flap debridement) and report that PD, CAL and IBD decrease more with the use of EMD after one year (Figures 1-3). The results are statistically significant. However, with respect to PD and CAL, the actual difference between EMD and control after one year is slightly less than 1mm for the study by Okuda, compared to approximately 2mm for the Francetti study (Table 5). The actual difference for IBD is approximately 1.5mm for the study by Francetti (Table 5). Okuda expressed the change in IBD from baseline to the end point as a percentage and did not provide actual measurements. Thus, the reader is unable to determine the actual IBD difference between EMD and the control, which is a limitation of this particular study.

Discussion

Based on this evidence-based report, the level of evidence is moderately high for the effectiveness of pharmaceutical components in bone replacement in invasive periodontal surgery. Every article examined in this review had the highest quality of evidence with Level I and Grade A classifications, and with critical appraisal scores ranging from 15 to 17.

According to Figures 1 and 2, the baseline PD and CAL values are uniform across the studies using DFDBA, PGF, and EMD. PD and CAL reduction was noted for both control and test groups. There is a greater PD decrease amongst test materials, with the exception of DFDBA. As well, there is a greater CAL decrease among test groups, with the exception of DFDBA and PGF. Figure 3 illustrates similar baseline IBD values for the control and test groups using DFDBA, PGF, and EMD. IBD decreased for both control and test groups for all materials however, the reduction was more marked for test groups. PD, CAL, and IBD are outcome measures that are commonly used in research for assessing periodontal regeneration are adequate references for comparing baseline to endpoint of hard and soft tissue measurements.

Table 5 contains the compiled data from all five studies for each of the outcome measures that were evaluated. The PD reduction for treatment relative to control ranges from -0.74 mm to 2.15 mm, demonstrating variation between the materials. Only DFDBA yields a negative result, implying that open flap debridement is better than the use of the pharmaceutical component. PGF and EMD display greater improvement in PD. CAL gain for treatment relative to control ranges from -0.87 mm to 1.75 mm, indicating differences between materials. The DFDBA study and the Howell study for PGF indicate greater CAL gain with open flap debridement compared to the test. Okuda '05 using PGF, and both EMD studies report a CAL gain with test compared to control. IBD improvement of the treatment relative to control ranges from 0.90 to 1.51 mm. All

the studies indicate a greater improvement of IBD with the use of pharmaceutical components over open flap debridement alone. Although most studies illustrate an overall decrease in PD, CAL and IBD with respect to the different materials used, there is variation in how much of an effect. The variability between the results for different materials can be due to the specific inclusion / exclusion criteria that the authors used in their studies, such as systemic complications

It is important to note that open flap debridement alone, without the addition of a pharmaceutical component, is effective in treating periodontal disease. A pharmaceutical component is inserted into the intra-bony defect after debridement. Generally, this results in a greater regeneration of periodontium compared to debridement alone. Open flap debridement with and without a pharmaceutical component is a routine procedure that is done with ease in a clinical setting.

Overall, the literature indicates that PGF and EMD show statistically significant results for bone regeneration. However, it should be noted that statistical significance may not represent clinical significance. As shown in Table 5, variability exists amongst PD, CAL and IBD reductions. The definition of clinical significance for these variables must be determined by the clinician, while considering the severity and effect of bone loss in their patients. Hence, variability in the judgement of clinical significance will exist within the field of periodontology.

In the Masters study employing DFDBA, fifteen subjects with moderate to advanced periodontitis were treated over a one year duration. A larger sample size and longer duration of study may demonstrate statistically significant differences between the DFDBA and the control group¹¹. The Masters study is not double blinded, suggesting potential bias of the examiners. The large standard deviation results from the large variability in patient response, which limits the

parameters of statistical analysis¹¹. PD and CAL error measurements could partially account for greater reduction in PD and CAL in the control group compared to the DFDBA group. Also, a limitation to this study is the variations in morphology of the defects (masters), and how they influence the regeneration potential. The number of osseous walls, the depth and width of the defects, and the adjacent root anatomy are variable, resulting in difficulty maintaining plaque control and further limiting the success of DFDBA treatment¹¹. Due to our exclusion criteria, articles prior to 1995 were not reviewed, and hence limited the availability of DFDBA studies.

For PGF, both studies of one year duration show improvement of bone regeneration after periodontal surgery. However, the findings are not consistent between these two studies. Howell reports significant bone regeneration with no soft tissue augmentation⁸. The researchers excluded the standard clinical PD measurement. In Okuda '05 the researchers state that PRP enhanced soft tissue gains in terms of PD and CAL reductions⁷. There was a 0.8 mm increase in IBD in the test group compared to control, but the difference was not statistically significant. When evaluated by critical appraisal checklist, Howell's study lost two points because duration of study is insufficient and not all clinically important outcomes were considered (PD measurement for angular lesions)⁸. And with a better study design and longer duration of study, Okuda' study ('05) scored 17/17⁷. Future studies with longer duration, larger sample size, and consistent techniques are desirable in evaluating the application of growth factors clinically after periodontal surgery.

Studies using EMD have limitations of small sample size, short duration and variable morphology of defects. Due to the small sample size, conclusions cannot be generalized to the entire population. Studies of longer duration would be ideal to see whether the statistically significant difference between EMD and control groups is maintained and whether there is

clinical significance for both EMD and control groups. The absolute difference between EMD and control for PD, CAL and IBD would be measured to determine if the values stay the same, or increase in favor of EMD, compared to values reported at one year. The study by Francetti reports that after 2 years, there is no statistical difference between EMD and control for PD¹³. This provides additional support for future studies to be of longer duration. The morphology of the defect is a factor that is more difficult to control as it depends on individual variation. It is unlikely to find large samples of people all with the same morphology of defect. Nonetheless, it is a limitation that must be considered.

Overall, the limitations of the studies include small sample size, short duration, and variability in morphology of defects. Histometric analysis may be ideal, however, was not feasible for ethical reasons. In cases where tooth extraction is inevitable, histology should be considered for analysis. The results of this report are limited to our definitions, specifically the nature of pharmaceutical components. Our results may not correlate with other studies due to our inclusion of osteoinductive materials, and exclusion of osteoconductive materials.

Conclusion

The evidence suggests that pharmaceutical components are effective in bone replacement after invasive periodontal surgery. In this evidence-based report, variability in the results may be due to specific inclusion / exclusion criteria that the authors of the studies used. Future studies should address the limitations stated above, as well as achieve reproducibility of results and standardize the sample population. Further studies taking these factors into consideration may yield stronger support for the use of pharmaceutical components in bone replacement. Although periodontal regeneration is ideal, repair still renders functional support to the dentition and thus, repair is adequate in treating patients with periodontitis. Therefore, pharmaceutical components are effective in bone replacement after invasive periodontal surgery, whether they achieve repair or periodontal regeneration.

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TABLES AND FIGURES

Table 1: Checklist to Assess Evidence of Efficacy of Therapy or Prevention¹⁰

1. Was the study ethical?
2. Was a strong study design used to assess efficacy?
3. Were outcomes (benefits and harms) validly and reliably measured?
4. Were interventions validly and reliably measured?
5. What were the results?
▪ Was the treatment large enough to be clinically important?
▪ Was the estimate of the treatment effect beyond chance and relatively precise?
▪ If the findings were “no difference”, was the power of the study 80% or better?
6. Are the results of the study valid?
▪ Was the assignment of patients to treatment randomized?
▪ Were all patients who entered the trial properly accounted for and attributed at its conclusion?
I) Was loss to follow up less than 20% and balanced between the test and controls?
II) Were patients analyzed in the groups to which they were randomized?
▪ Was the study of sufficient duration?
▪ Were patients, health care workers, and study personnel “blind” to treatment?
▪ Were the groups similar at the start of the trial?
▪ Aside from the experimental intervention, were the groups treated equally?
▪ Was care received outside the study identified and controlled for?
7. Will results help care for patients?
▪ Were all clinically important outcomes considered?
▪ Are the likely benefits of treatment worth the potential harms and cost?

Table 2: List of Articles Eliminated after Critical Appraisal

Material	Study	Reason for Rejection
DFDBA	Flemmig '98	No raw data provided.
	Gouldin '96 ¹⁴	Used Guided tissue regeneration (GTR) and an osteoconductive material
	Gurinsky '04 ¹⁵	Multiple treatment modality, with Enamel Matrix Derivative
	Laurell '98 ¹⁶	Review article, not specific study
	Lovelace '98 ¹⁷	Multiple treatment modality, with Bioactive Glass
	Mellado '95 ¹⁸	Used an osteoconductive material
	Mellonig '96 ¹⁹	Review article, not specific study
	Trejo '00 ²⁰	Had no control group
PGF	Camargo '05 ²¹	Included smoking patients; and used GTR as well
	Hanna '04 ²²	Small sample size
	Nevins '03 ²³	Small sample size
EMD	Froum' 01 ²⁴	No double blind
	Kalpidis '02 ²⁵	Review article, not a specific study
	King '01 ²⁶	Review article, not a specific study
	Sanz '04 ²⁷	Used GTR as well
	Scheyer '02 ²⁸	Had no control
	Schulean '02 ²⁹	Combination treatment with EMD
	Sculean '01 ³⁰	Used GTR as well
	Trombelli '02 ³¹	Systematic review, not a specific study
	Zucchelli '03 ³²	Combination treatment with EMD

Table 3: Articles Presenting Evidence for the Effectiveness of Pharmaceutical Components for Bone Regeneration after Periodontal Surgery

Author, Year, Pharm. Component	Study Design and Critical Appraisal Score	Population (n, sex, age group, place, disease status)	Calibration/ Reliability	Test Treatment	Control treatment	Outcome and statistical significance		Conclusion, Strength of evidence and classification, critical appraisal comments
						Measurements	p value	
- Francetti - 2004 - EMD	- RCT - Double blind - 17/17	- 24 pts - 11 male, 13 female - mean age: 46.5 ± 11.2 - Milan (university dental clinic) - Disease status not reported	- Single examiner for all clinical measurements - Single operator for all surgery - Customized bite blocks for reproducible x-rays - X-rays evaluated by single blind examiner	12 pts were treated with EMD and OFD	12 pts were treated with OFD	PD Reduction at 12 mths	p<0.01	- EMD enhances periodontal regeneration rate in Tx of angular bony defects - Level I Evidence, Grade A Classification
						CAL Gain at 12 & 24 mths	p<0.01	
						IBD Reduction at 12 & 24 mths	p<0.01	

TABLE 3 cont'd

Author, Year, Pharm. Component	Study Design and Critical Appraisal Score	Population (n, sex, age group, place, disease status)	Calibration/ Reliability	Test Treatment	Control treatment	Outcome and statistical significance		Conclusion, Strength of evidence and classification, critical appraisal comments
						Measurements	p value	
<ul style="list-style-type: none"> - Okuda - 2000 - EMD 	<ul style="list-style-type: none"> - RCT - Double blind - Split mouth - 17/17 	<ul style="list-style-type: none"> - 16 pts - 8 male, 8 female. - Mean age 56 ± 11 - Nigatta (university dental clinic) - Moderate to advance periodontitis 	<ul style="list-style-type: none"> - Clinical measurements by single examiner - Use of pressure sensitive perio probe with 20g controlled probing force - surgical debridement & placement of EMD/placebo independent - Customized bite blocks for reproducible x-rays 	<ul style="list-style-type: none"> 16 pts were treated with EMD and OFD ↳ 14 with 1 site ↳ 2 with 2 sites 	<ul style="list-style-type: none"> 16 pts were treated with placebo and OFD ↳ 14 with 1 site ↳ 2 with 2 sites 	PD Reduction at 12 mths	p<0.05	<ul style="list-style-type: none"> - EMD Tx compared to placebo demonstrates a favorable response on diseased root surfaces associated with intrabony osseous defects - Level I Evidence, Grade A Classification
						CAL Gain at 12 mths	p<0.05	
						IBD Reduction at 12 mths	p<0.05	

TABLE 3 cont'd

Author, Year, Pharm. Component	Study Design and Critical Appraisal Score	Population (n, sex, age group, place, disease status)	Calibration/ Reliability	Test Treatment	Control treatment	Outcome and statistical significance		Conclusion, Strength of evidence and classification, critical appraisal comments
						Measurements	p value	
- Okuda - 2005 - PGF	- RCT - Double blind - Split mouth - 17/17	- 70 pts - 49 male, 21 female - mean age: 55.5±8.2 - Nigatta, (university dental clinic) - Moderate to advanced chronic periodontitis	- A calibrated color-coded periodontal probe to the nearest mm and customized acrylic stents with a guiding groove were applied to ensure highly reproducible clinical measurements	- 35 pts were treated with PRP and HA	- 35 pts were treated with Saline and HA	PD Reduction at 12 mths	p<0.05	- Both treatment modalities were effective in improving clinical and radiographic parameters. - The PRP+HA treatment statistically significant increased PD reduction and CAL gain compared to the control group - Level I Evidence, Grade A Classification
						CAL Gain at 12 mths	p<0.01	
						IBD Reduction at 12 mths	p>0.05	

TABLE 3 cont'd

Author, Year, Pharm. Component	Study Design and Critical Appraisal Score	Population (n, sex, age group, place, disease status)	Calibration/ Reliability	Test Treatment	Control treatment	Outcome and statistical significance		Conclusion, Strength of evidence and classification, critical appraisal comments
						Measurements	p value	
- Howell - 1997 - PGF	- RCT - Double blind - Split mouth - 15/17	- 38 pts - 25 male, 13 female - mean age: 46.1 - Harvard University and the University of North Carolina - Moderate to sever periodontal disease	- All clinical measurements in this trial were obtained by a single masked examiner who was calibrated prior to the study for 95% agreement (i.e. ± 1 mm) for both soft and hard tissue outcomes	- 16 pts treated with 50ug/ml rhPDGF-BB/rhIGF-I and OFD (LD group) - 14 pts treated with 150ug/ml rhPDGF-BB/rhIGF-I and OFD (HD group)	- 19 pts treated with OFD alone - 19 pts treated with vehicle and OFD	CAL Gain in LD group at 6 months	p>0.05	- No safety issues which resulted from the use of the drug - Significantly greater bone formation occurred in osseous defects treated with 150ug/ml rhPDGF-BB/rhIGF-I and OFD - Level I Evidence, Grade A Classification
						IBD Reduction in LD group at 6 months	p>0.05	
						CAL Gain in HD group at 9 months	p>0.05	
						IBD gain in HD group at 9 months	p<0.05	

TABLE 3 cont'd

Author, Year, Pharm. Component	Study Design and Critical Appraisal Score	Population (n, sex, age group, place, disease status)	Calibration/Reliability	Test Treatment	Control treatment	Outcome and statistical significance		Conclusion, Strength of evidence and classification, critical appraisal comments
						Measurements	p value	
- Masters - 1996 - DFDBA	- RCT - Split mouth - 15/17	- 15 pts - 3 males, 12 females - aged 35 to 61 - moderate-advanced adult periodontitis	- Fixed reference points - Standardized perio probe (Michigan probe) at 8 sites on each tooth - surgical debridement - Recall at 3, 6, and 12 months - Standardized radiographs - Computer assisted radiographic evaluation (CARE) for radiographic analysis	15 pts were treated: 1 site with DFDBA and OFD	15 pts were treated: 1 site with OFD	PD Reduction at 12 mths	p>0.05	- There is no benefit from DFDBA when grafting osseous defects - Level I Evidence, Grade A Classification
						CAL Gain at 12 mths	p>0.05	
						IBD Reduction at 12 mths	p>0.05	

*OFD – Open Flap Debridement

Table 4: Definitions of Outcome Measures Evaluated in this Report

Outcome Measure	Definition
PD	Pocket depth is from the free gingival margin to base of pocket.
CAL	Clinical attachment loss is defined as CEJ-PD, which is the measurement from the cemento-enamel junction (CEJ) to the base of the pocket.
IBD	Intra-Bony Defect Depth is defined as AC-BD, where AC is from the CEJ to the alveolar crest and BD is from the CEJ to the depth reference.

Table 5: Raw Data Reproduced from the Chosen Articles for PD, CAL and IBD at Baseline, Endpoint, and with Calculated Enhancement

Material	Study	PD Baseline (mm)		PD Endpoint (mm)		PD Reduction (mm)		
		Control	Treatment	Control	Treatment	Control	Treat	Enhancement
DFDBA	Masters '96	7.00±1.25	6.73±1.39	3.53±0.99	4.00±1.07	3.47	2.73	-0.74
PGF	Okuda '05	7.90±1.80	7.70±1.50	4.20±1.90	3.00±0.80	3.70	4.70	1.00
EMD	Okuda '00	6.22±0.73	6.33±0.91	4.00±1.03	3.39±0.85	2.22	2.94	0.72
	Francetti '04	6.71±1.25	7.86±1.46	4.14±1.86	3.14±0.90	2.57	4.72	2.15
		CAL Baseline (mm)		CAL Endpoint (mm)		CAL Gain (mm)		
		Control	Treatment	Control	Treatment	Control	Treat	Enhancement
DFDBA	Masters '96	7.33±1.50	7.33±2.02	4.93±1.22	5.80 ±1.57	2.40	1.53	-0.87
PGF	Howell '97	6.41±0.47	6.63 ± 0.50	4.43*	5.11*	1.98	1.52	-0.46
	Okuda '05	8.80±1.80	8.4 ± 1.80	6.80± 1.70	5.00 ±1.80	2.00	3.40	1.40
EMD	Okuda '00	6.83±1.20	6.72±1.13	6.00±1.28	4.94±1.00	0.83	1.78	0.95
	Francetti '04	8.29±1.60	9.43±1.13	6.00±1.91	5.29±1.11	2.29	4.14	1.85
		IBD Baseline (mm)		IBD Endpoint (mm)		IBD Reduction (mm)		
		Control	Treatment	Control	Treatment	Control	Treat	Enhancement
DFDBA	Masters '96	3.87±0.92	4.2±1.66	1.53± 1.19	0.93±1.16	2.34	3.27	0.93
PGF	Howell '97	4.18±0.36	4.25±0.38	3.43 *	2.17 *	0.75	2.08	1.33
	Okuda '05	4.8±1.70	5±1.6	2.1±1.7	1.4±1.3	2.70	3.60	0.90
EMD	Francetti '04	4.81± 0.58	5.93±1.25	3.37± 0.86	2.98± 0.74	1.44	2.95	1.51

* Standard deviation was not reported in the studies

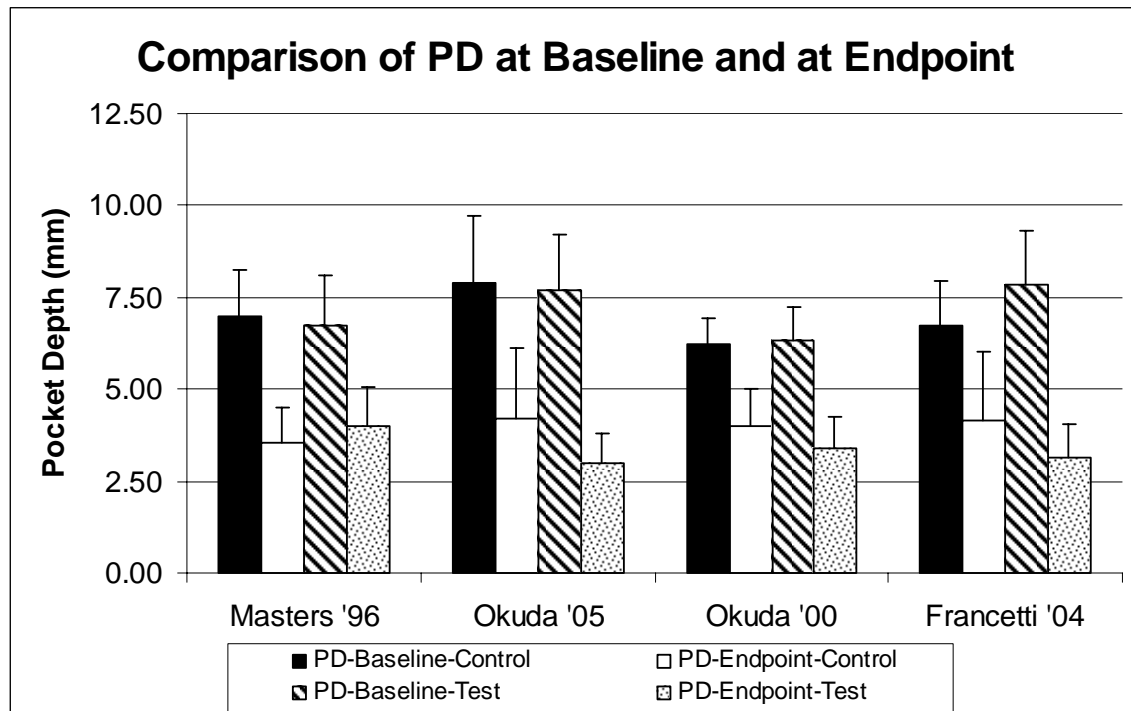
Figure 1: Comparison of Pocket Depth at Baseline and Endpoint of Study Duration

Figure 2: Comparison of Clinical Attachment Loss at Baseline and Endpoint of Study Duration

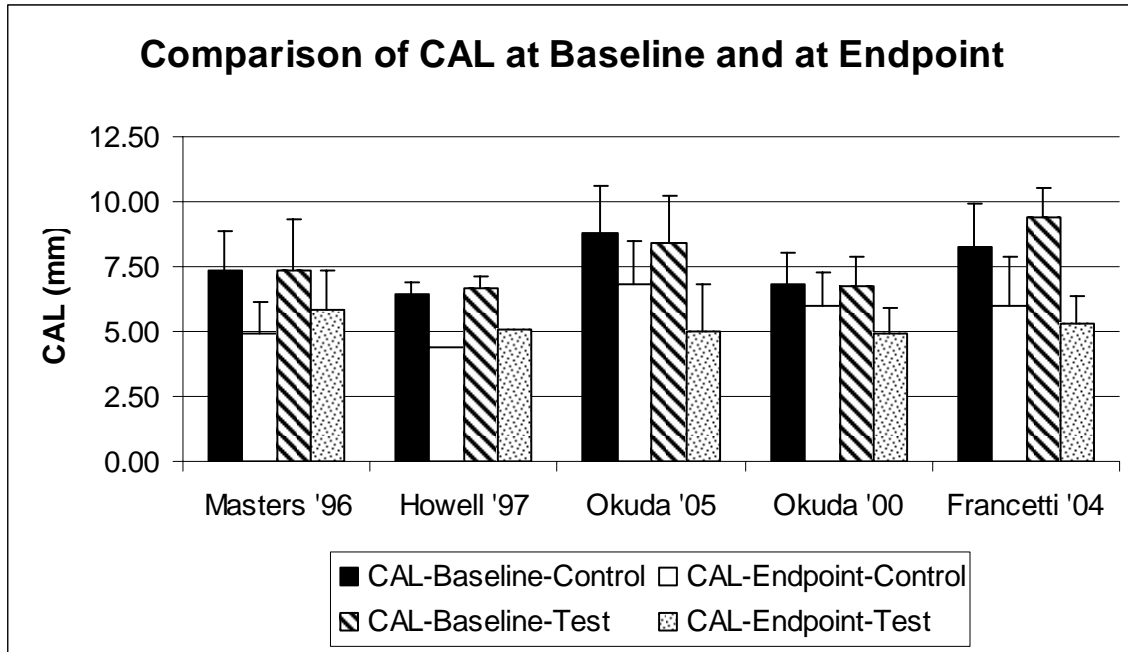
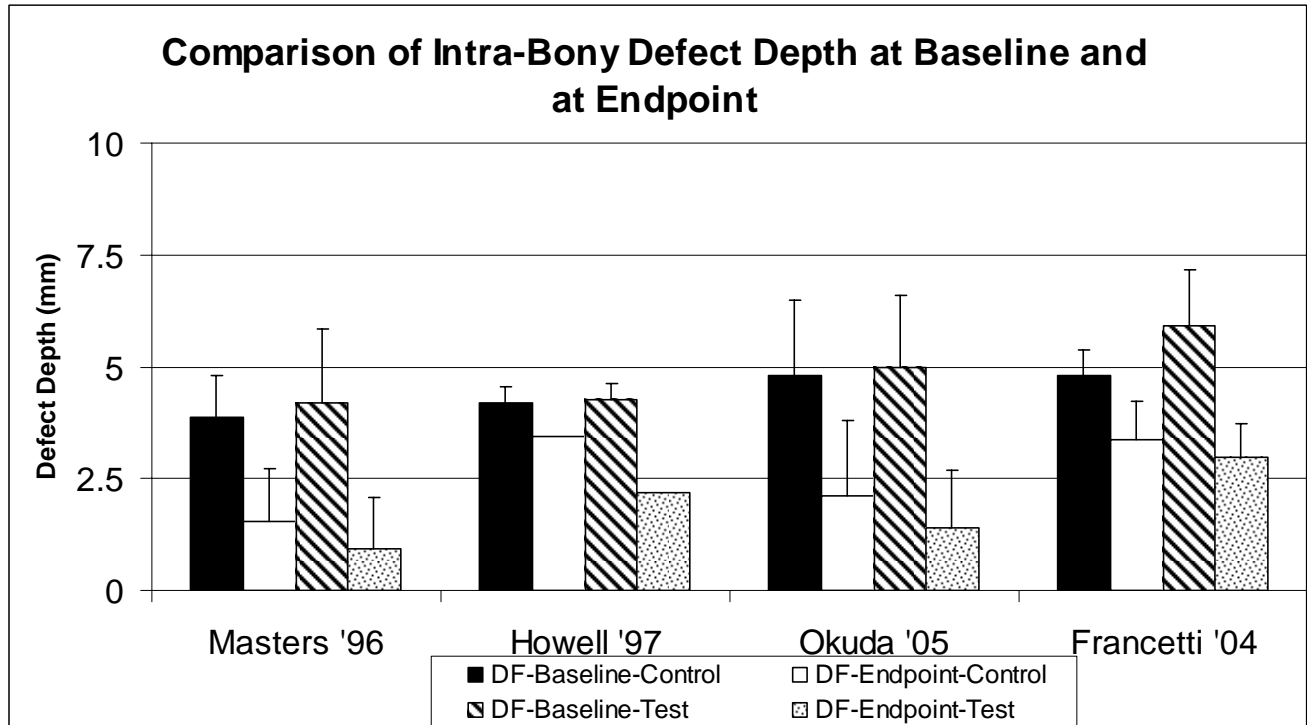


Figure 3: Comparison of Intra-bony Defect Depth at Baseline and Endpoint of Study Duration



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