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Review

Regeneration of the Periodontal Apparatus in Aggressive Periodontitis Patients

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Abstract: The aim of this article is to evaluate and compare, retrospectively, the efficacy of two regenerative periodontal procedures in patients suffering from aggressive periodontitis (AgP). Twenty-eight patients were diagnosed with AgP, suffering from multiple intra-bony defects (IBD); that were treated by one of two regenerative modalities of periodontal therapy randomly assigned to each patient: a. guided tissue regeneration (GTR) or b. an application of enamel matrix derivatives (EMD) combined with DBX. The monitoring of the treated sites included recordings of probing depth (PD), clinical attachment level (CAL), and gingival recession. Pre-treatment and follow-up (up to 10 years from the surgery) recordings were analyzed statistically within and between groups. A significant reduction was shown at time on PD and CAL values, however, not between subject groups. CAL values decreased in all sites. At EMD group (44 sites) CAL gain was 1.92 mm (±1.68) from pre-treatment to follow-up ($p<0.001$) and at the GTR group (12 sites) CAL gain of 2.27 (±1.82) mm. In conclusion, 1-10 years observations have shown that surgical treatment of AgP patients by either GTR or by application of EMD/DBX results in similar successful clinical results.

Keywords: Periodontal regeneration; Aggressive periodontitis; Deproteinized bovine bone; enamel matrix derivatives (Emdogain®); guided tissue regeneration (GTR).

1. Introduction

Aggressive periodontitis (AgP) is a periodontal disease characterized by a rapid loss of periodontal tissue. Several features describe AgP, such as early onset, involvement of a few or multiple teeth, and a relatively rapid progression. (Baer 1971; Armitage 1999). There are two distinguishable patterns available: Localized form that involves the first molars and the incisors and up to two additional teeth, and Generalized form with an extensive destructive pattern (Baer & Socransky 1979, Hørmand & Frandsen 1979, Armitage 1999). Recently (Tonetti et al 2018), the classification of the periodontal entities has been updated to stages (I – IV) and grades (A – C). The stages are based on periodontal breakdown severity, management complexity and the extent of the disease. Grade definitions are based on the progression which in principal related to risk factors. Practically, most of the AgP cases would be classified as stage III grade B or C.

There is an assumption that the main contributing factors are quantitatively and qualitatively related to alterations in the immune response (Khocht & Albandar 2014), host-environment interactions and intra-host gene (Albandar 2014; Vieira & Albandar 2014) and there is ethnic attribution whereas AgP is more frequent in certain geographic regions (Albandar 2014; Susin et al 2014).

The therapy goal of AgP is to completely prevent and stop the progression of the disease, to maintain health and to regenerate the lost deprived periodontium; these goals are similar to those of chronic adult periodontitis (Armitage 1999). Systematic reviews (Deas & Mealy 2010; Nibali et al 2013) claimed that the mechanical therapy may be comparable in both conditions.

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Two different approaches may accomplish regenerative periodontal therapy: a. Guided tissue regeneration(GTR) - by selective cell population using tissue barriers (Gottlow et al 1986) or b. Enamel matrix derivates (EMD) - application of tissue morphogenic factors to promote tissue growth (Hammarström 1997; Heijl et al 1997).

Some trails were performed in order to test the combination of EMD with deproteinized bone xenograft (DBX) in the belief that it may have certain qualities of a bioactive bone graft (Lekovic et al 2000, 2001a; Camargo et al 2001; Scheyer et al 2002; Velasquez-Plata et al 2002; Sculean et al 2002, 2003a, 2005, 2008a; Döri et al 2005; Zucchelli et al 2003; Yamamoto et al 2007; Iorio-Siciliano et al 2014; Farina et al 2014). On the other hand, previous studies that used critical size defect in rats failed to support these claims(Donos et al 2004, 2005, 2006). Also, in meta-analyses (Tu et al 2010; Verardi 2012), a significant contribution of this combination could not be proved. However, Miron et al 2012 have shown that EMD enhance osteoblast and PDL cell proliferation, differentiation and attachment to DBX particles in-vitro. In-vivo recent data (Miron et al 2014) has shown that EMD combined with DBX particles has ability to enhance the speed of new bone formation in rat osseous defects.

Many randomized trials have shown encouraging results of periodontal therapy in ChP patients, however, there are only a few reports that claim clinical success using either GTR technique in AgP patients (Sirirat et al 1996; Zucchelli et al 2002a; Buchmann et al 2002) or EMD application (Kiernicka et al 2003; Bonta et al 2003; Miliauskaite et al 2007; Kaner et al 2009). Moreover, most of these reports, especially those related to the later, are based on small group of patients with no clinical standardization and/or follow-up protocols.

In this study, AgP patients were treated via one of the surgical regenerative options, GTR or EMD w/wo biomaterial filler, and later their outcome were compared.

2. Periodontal regeneration procedures

2.1. Guided Tissue Regeneration (GTR) procedure (Figures 1-2)

Prior surgery, patients were admitted to rinse their mouth with 0.2% Chlorohexidine, followed by local anesthesia, buccal and lingual infiltration. Muco-periosteal flaps were reflected in order to expose widely the intra-bony defects, while preserving the interproximal soft tissue using the papillary preservation technique (PPT) described by Takei et al (1985, 1989) and Cortellini et al (1995). Horizontal interproximal incision was performed on the opposite side (buccal or lingual) considering the site with the deepest PD value. Root planning and soft tissue debridement was conducted to smooth the exposed root surface.

A dummy matrix was trimmed to prepare a customized fit resorbable collagen membrane (Figures. 1,2, case #4). DBX particles (500-1000µ) were placed to fill the intra bony defect, followed by coverage with the trimmed membrane. Primary soft tissue closure was achieved by releasing the flaps and stabilizing it ,executing interrupted internal mattress sutures to achieve complete closure in the interproximal areas (Cortellini et al 2001).

2.2. Periodontal regeneration by application of Enamel Matrix Derivatives (Figures 3-5)

Prior surgery, patients were admitted to rinse their mouth with 0.2% Chlorohexidine, followed by local anesthesia, buccal and lingual infiltration. Muco-periosteal flaps were reflected in order to expose widely the intra-bony defects, while preserving the interproximal soft tissue using the papillary preservation technique (PPT) described by Takei et al (1985, 1989) and Cortellini et al (1995). Horizontal interproximal incision was performed on the opposite side (buccal or lingual) considering the site with the deepest PD value. Root planning and soft tissue debridement was conducted to smooth the exposed root surface.

The exposed roots were conditioned with 24% EDTA for 2 minutes, followed by saline rinsing, and by applying EMD gel (Emdogain®) (Figs. 3,4, Case #2). Effort was made to avoid bleeding in these sites. In some cases, DBX, soaked in EMD gel were then added to fill the defect. Primary soft

tissue closure was achieved by releasing the flaps and stabilizing it, executing interrupted internal mattress sutures to achieve complete closure in the interproximal areas (Cortellini et al 2001).

Strict post-op instructions were given to candidates from both groups. At 2 weeks, sutures were removed. Patients were instructed to gently swab the site with gauze soaked in CHX solution. During maintenance phase, for the first month, patients were monitored weekly, followed by monthly visits for half a year, and once every three months later. Recall visits focused on reinforcement of OHI and supra-gingival prophylactic cleaning. Proving depth (PD), clinical attachment level (CAL) and recession height (Rec) were recorded at 6, 12, month post-surgery. Peri-apical and bite-wings radiographs were taken at the initial examination and after 6 and 12 months. However, since no verification of standardized location and angulation of the radiographs, only an observational evaluation has been made.

2.3. Materials and methods

Periodontal parameter evaluation

Tel Aviv University ethic committee approved this study.

28 patients that were diagnosed with AgP randomly selected. 6 patients (12 surgical sites) were treated by GTR method, and therefore called GTR group. 12 patients (54 surgical sites) were treated by EMD method, and therefore called EMD group.

First visit included extra and intra oral examinations including, a thorough periodontal chart, full mouth peri-apical radiographs and study models.

PD, CAL, and height of exposed roots (Rec) were recorded in all destructed sites. As performed in previous study (Artzi et al, 2015), at each periodontally involved interproximal/inter-radicular intra-bony site, the deepest probing depth was recorded. Mean PD and CAL (Tables 1-2) represent the execution of the average measurements of all sites of each treated IBD in each patient. For example, in a given interproximal IBD, mean probing depth was calculated as the average of the disto-buccal, disto-lingual/palatal of the mesial root (tooth) surface and the mesio-buccal and mesio-lingual/palatal of the distal root (tooth) surface. Therefore, each mean PD site represents only the involved IBD without the neighboring unaffected shallow ones. Horizontal furcation involvement was assessed, in the inter-radicular areas (Hamp et al 1975). Plaque score index (PI, Turesky et al 1970) and Bleeding on probing (BOP, Saxer & Mühlemann 1975) were monitored carefully. During each re-evaluation visit these parameters repeated.

All patients went through a meticulous non-surgical periodontal treatment phase including oral hygiene instructions and training, full mouth scaling and root debridement in conjunction with systemic antibiotics of Amoxicillin 500mg + Metronidazole 250mg (TID) for a week (van Winkelhoff et al 1989, Guerrero et al 2005, Herrera et al 2002).

3. Results

Considering the strict oral hygiene maintenance program, patient compliance was very satisfactory. No adverse effects were noted throughout either mode of treatment. In 3 patients, a distinctive familial inheritance along their family tree was noted. However, they responded to treatment was immaculate.

Periodontal indices were re-measured, upon re-evaluation of the non-surgical phase. Practically, a clinical improvement was evident as related to the periodontal indices. Tables 1 and 2 show PD reduction and CAL gain at follow-up, up to 10 years post the completion of the surgical phase. Since there was no significant approval on the PD and CAL indices at the extensive IBD sites, the baseline clinical and follow-up, 10 years recordings CAL indices listed in the Tables.

Follow -up (up to 10 years) PD in the GTR group (n=6; sites = 12) was reduced from 6.23 mm (±1.24, SD) to 3.875 mm (±1.02). Mean PD reduction was 2.35 mm ($p<0.001$). Mean CAL in the GTR group reduced from 6.375 (± 1.37) to 4.1 mm (± 1.06); mean CAL gain was 2.27 mm ($p<0.001$).

In the EMD group (n=22; sites = 54), mean PD reduced from 5.58 mm (± 1.34) to 3.64 mm (± 1.36). Mean reduction was 1.95 mm ($p<0.001$). Mean CAL was reduced from 6.16mm (± 1.52) to 4.26) mm

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(± 1.3); mean CAL gain of 1.92 mm ($p<0.001$). Within each group, PD reduction and CAL gain between the measurements were statistically significant.

However, tests of between subjects (GTR and EMD) effects, showed no statistical difference in regard to PD ($p>0.005$) nor to CAL ($p>0.005$).

3.2. Figures, Tables and Schemes

Figure 1. Case # 4 of the GTR group, upper left sextant. The pre surgery periapical radiograph (a) demonstrates an extensive periodontal destruction around on the mesial aspect of the first molar. (b) Periodontal probe shows a 2-wall intrabony component of 7mm, who was filled by BBM particles (c) and covered by a collagen membrane (d). two years follow-up periapical radiograph (e) shows bone filling around on the first molar.

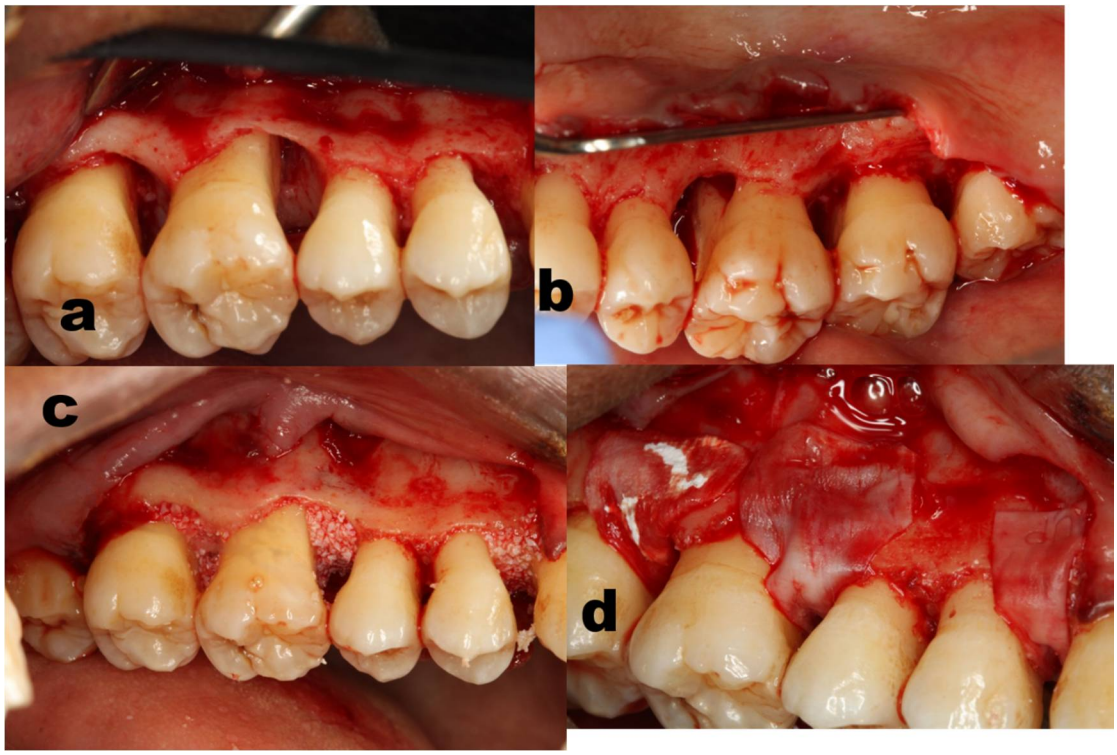

Figure 2. Case # 4 of the GTR group, upper right sextant. (a,b) Buccal and palatal view of the crestal bone topography. BBM particles inserted to fill the defects (c) followed by overlay resorbable collagen membranes (d).

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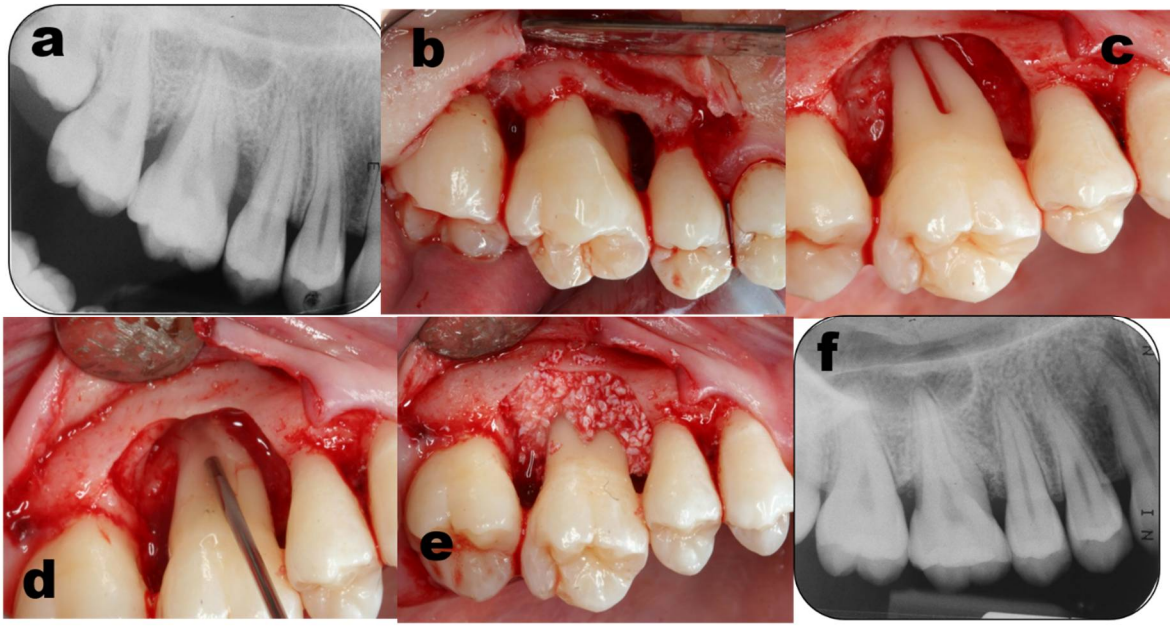

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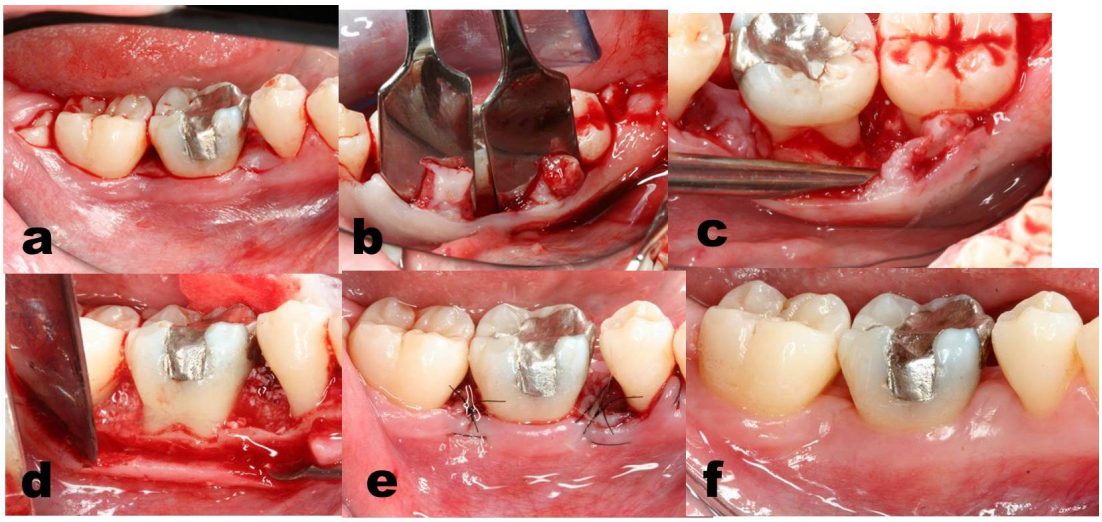
158 **F**igure 3. Case # 2 of the EMD group, upper right sextant. Pre surgery periapical radiograph (a)
159 shows an extensive periodontal destruction around on the distal aspect of the first molar. Buccal (b)
160 and palatal (c) aspects of the debrided roots. EMD gel was applied along the exposed roots (d)
161 followed by BBM particles as a bio-material filler(e). four years follow-up periapical radiograph (f)
162 shows bone filling around the first molar.



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164 **F**igure 4. Case # 2 of the EMD group, lower right sextant. Papillary preserve technique flap elevation
165 technique (a, b) performed to exposed the periodontal defect (c). EMD gel was applied on the
166 debrided roots followed by BBM particles (d). In order to obtain full soft tissue closure the flaps were
167 sutured (e). At 1 month, immaculate healing was evident (f). In order to achieve full closure, note the
168 preservation performed of the interproximal col tissue (b), subsequently.

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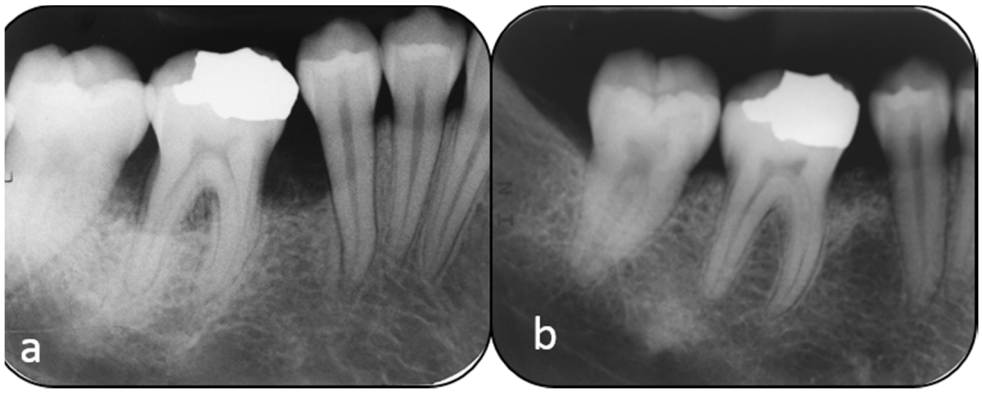

Figure 5. The Pre(a) and Post(b) periapical radiographs of Case #2 of the EMD group, lower right first molar. Note the bone filling on the mesial and distal aspect of the lower right first molar.

Table 1. GTR group, Pre-op and Follow-up periodontal probing depth (PD) mean measurements.

site	PD pre	CAL pre	PD curr	CAL curr	PDR[1]	CAL GAIN
1	5.5	5.5	5	5	0.5	0.5
2	6.5	7	3.5	4.25	3	2.75
3	4	4	2	2	2	2
4	5.5	5.5	5.5	5.5	0	0
5	4.5	4.5	5.25	5.5	-0.75	-1
6	7	7.5	4.75	4.75	2.25	2.75
7	6.5	6.5	3.5	3.5	3	3
8	6	6	3.75	3.75	2.25	2.25
9	7.5	8	2.75	2.75	4.75	5.25
10	8.5	8.75	3	3.25	5.5	5.5
11	7.5	7.5	3.5	5	4	2.5
12	5.75	5.75	4	4	1.75	1.75
Average[2]	6.23	6.37	3.87	4.10	2.36	2.27
SD	1.24	1.37	1.02	1.06	1.79	1.82

[1]PDR – Probing Depth Reduction

[2] The average of 4 probing depth measurements at the disto-buccal, mesio-buccal, mesio-lingual and disto-lingual of each given IBD site.

Table 2. EMD group, Pre-op and Follow-up periodontal probing depth (PD) mean measurements..

site	PD pre	CAL pre	PD curr	CAL curr	PDR[1]	CAL GAIN
1	5	5.5	3	3.5	2	2
2	4.75	5.75	2.25	3.75	2.5	2
3	3.75	3.75	3	3.75	0.75	0
4	7	7	2.75	3.75	4.25	3.25
5	4	4	4.5	4.5	-0.5	-0.5
6	6.5	6.5	4.25	4.25	2.25	2.25
7	4.5	4.5	3.75	3.75	0.75	0.75

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8	5.5	5.5	6.5	6.5	-1	-1
9	5.5	5.5	3.75	3.75	1.75	1.75
10	5	5	3	3	2	2
11	6	6.75	6	6.75	0	0
12	8	8	6.5	7.25	1.5	0.75
13	7	7	3.25	4.5	3.75	2.5
14	6.5	9	2	4	4.5	5
15	5	6.5	4	6	1	0.5
16	7.5	10.25	3.25	5.75	4.25	4.5
17	4.5	6	3.25	4.25	1.25	1.75
18	5.75	5.75	2.25	2.25	3.5	3.5
19	5	5	3.5	3.5	1.5	1.5
20	7.5	8	6	6	1.5	2
21	4.5	5	4.5	4.5	0	0.5
22	7.5	7.5	3	4	4.5	3.5
23	3.5	5.25	2	3.25	1.5	2
24	5.5	5.5	7	7	-1.5	-1.5
25	6.5	7	6.25	6.75	0.25	0.25
26	4	4.5	2.5	4	1.5	0.5
27	4.5	5	3.5	3.5	1	1.5
27	5.25	7.25	2.5	3.5	2.75	3.75
29	4	6.5	3	5.25	1	1.25
30	4.75	6	2	2.5	2.75	3.5
31	7	8	3.25	3.75	3.75	4.25
32	4.75	4.75	3.25	4.25	1.5	0.5
33	6	6	3.5	4.5	2.5	1.5
34	6.75	7.5	4.75	5.75	2	1.75
35	6.25	7.25	5.25	5.75	1	1.5
36	6.75	6.75	4	4	2.75	2.75
37	6.75	6.75	4	4	2.75	2.75
38	6.5	6.75	7	7	-0.5	-0.25
39	5.5	6	extracted			
40	8.75	9	3	3	5.75	6
41	8.5	8.75	3	3	5.5	5.75
42	3.75	3.75	2	3	1.75	0.75
43	6	6	2	3	4	3
44	4.75	5	2.25	2.75	2.5	2.25
45	5.5	6.5	2	2.5	3.5	4
46	7	9	3.25	4.25	3.75	4.75
47	4	5.75	5.25	5.75	-1.25	0

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48	4.25	4.25	3	3.5	1.25	0.75
49	4	5	2.75	3.75	1.25	1.25
50	4.25	4.25	3.5	3.5	0.75	0.75
51	4	4	3.25	3.25	0.75	0.75
52	3.5	3.5	2.75	2.75	0.75	0.75
53	5.75	5.75	3	3.25	2.75	2.5
54	7	7.75	3.75	3.75	3.25	4
Average[2]	5.58	6.16	3.64	4.24	1.94	1.92
SD	1.34	1.52	1.35	1.3	1.64	1.68

[1]PDR – Probing Depth Reduction.

[2] The average of 4 probing depth measurements at the disto-buccal, mesio-buccal, mesio-lingual and disto-lingual of each given IBD site.

4. Discussion

There are two different methods to support periodontal regeneration: Guided tissue regeneration (GTR) and amelogenin derived protein (EMD) applications. In spite of the differences between the two methods and the associated biological processes, the similar results achieved in AgP patients are of utmost importance.

In the present study, GTR treated sites presented PD reduction and CAL gain of 37.7% and 35.6 %, respectively. EMD sites showed similar results with PD reduction and CAL gain of 34.9 % and 31.2 %, respectively. Follow-up radiographs supported the clinical measurements, showing consistent bone augmentation and re-formation of lamina dura and periodontal ligament space (Figures 1,3,5).

It is well known that the IBD morphology has a determinant effect on the regeneration capacity. Thus, other shortcomings of the study design could be the fact that different IBD configurations were not considered as a variable factor in the interpretation of the outcome where they should be.

In order to achieve successful healing several indications are required; wound stability, re-vascularization, and the establishment of complete soft tissue closure; in regenerative treatment these are mandatory requirements for successful results. It has further been shown that flap management via PPT enhances the outcome of regenerative procedures (Cortellini et al 2001; Zucchelli et al 2002b). For these reasons we used those clinical measures in both groups.

It seems that in addition to meticulous surgical execution, strict maintenance and patient compliance are key factors, regardless the surgical mode of operation.

As specified, AgP is a rapidly progressing inflammatory disease. However, devoted care may result in quite predictable long term success (Buchmann et al 2002; Baumer et al 2011; Nibali et al 2013; Theugel et al 2014).

ChP and AgP have shown distinctive different etiological/contributing factors, the second being more aggressive, rapid and severe (Albandar 2014). For that reason, it is encouraging that the effectiveness of regenerative periodontal treatment of intrabony defects in AgP, allows successful and maintainable periodontal status.

It has been claimed that in severe chronic periodontitis GTR and EMD result in periodontal restitution (Gottlow et al 1986; Sculean et al 1999a,b,c, 2000a,b, 2001a,b, 2002, 2003a,b, 2004a,b, 2005, 2006; 2007, 2008a,b; Tonetti et al 2002, Trombelli et al 2002, Zucchelli 2002b, 2003; Windisch et al 2002; Sanz et al 2004; Cortellini & Tonetti 2005; Palmer et al 2008; Esposito et al 2009; Koop et al 2012; Tu et al 2012; Döri F et al 2013). Surprisingly, there is not enough data available regarding AgP (Vandana et al 2004; DiBattista et al 1995). However, some studies claim for successful results using either GTR procedures (Sirirat et al 1996) or EMD application (Zucchelli et al 2002a). Enamel matrix

proteins in cases of ChP seems to support wound healing and new periodontal tissue formation in IBD sites in AgP cases as well.

One can assumed that although consensus reports (Palmer et al 2008) as well as systematic reviews (Esposito et al 2009) did not differentiate between IBD treatment modality of patients diagnosed with AgP and/or ChP cases, that these sites successfully healed and maintained.

If we implicate laboratory research to our research, our findings are well consistent. No statistically significant differences in immunologic and microbial parameters between subjects with AgP and ChP has been presented in several reports (Rescala et al 2010). The population of that study showed comparable clinical outcome after treating ChP and AgP patients in a non- surgical approach (Rosalem W et al 2011). Another review performed by Deas and Mealy (2010) agreed that long term outcome could be comparable with blurred boundaries in ChP and Agp.

Although few reports examined the efficacy of regenerative procedures using GTR techniques in AgP patients, there is no accepted statement regarding it (DiBattista et al 1995; Sirirat et al 1996; Buchmann et al 2002; Zucchelli et al 2002a; Sant'Ana et al 2009; Lu et al 2012), or EMD application (Manor 2000; Bonta et al 2003; Vandana et al 2004; Miliauskaite et al 2007; Kaner et al 2009).

Combining GTR with a biomaterial grafting material (Trombelli et al 2002, Stavropoulos & Karring 2005; Iorio-Siciliano et al 2014) or EMD and a biomaterial (Lekovic V et al JOP 2000, 2001a,b; Camargo et al 2001; Scheyer et al 2002; Velasquez-Plata et al 2002; Sculean et al 2002, 2003a, 2005, 2008a; Döri et al 2005; Zucchelli et al 2003; Iorio-Siciliano et al 2014) have been extensively investigated showing that the addition of a xenograft such as DBX resulted in encouraging results in IBD in ChP. Thus, this would be related to the excellent biomaterial biocompatible and conductive properties rather than to the unproven induction as shown earlier (Donos et al 2004, 2005, 2006).

Esposito et al (2009), in a Cochrane systematic review, stated that there was no evidence of clinically significant differences between GTR and EMD in periodontal intra-bony lesions. However, it was found that the use of bone substitute materials procedures were less associated with soft tissue marginal recession compared with the application of EMD solely.

Practically, there is great significance of adding the biomaterial (DBX) whether in GTR and/or EMD technique in order to provide maintenance of the volume of the filled defect (Lindhe et al 2014) and thus, enhances the clinical outcome.

In the EMD group, no selective barrier was used, it can be assumed that the added biomaterial particles gave mechanical support to the soft tissue over-lay during the healing phase.

Supporting our previous study (Artzi et al. 2015) both therapy modalities are proven to achieve comparable clinical outcome i.e. stability of the soft tissue position, minimal recession and ease the ability of plaque control performance.

In conclusion, it appears that successful regenerative approach treatment can be achieved in a predictable manner in AgP patients. The key seems to be the meticulous treatment mode, for both techniques followed by a strict supportive periodontal maintenance.

5. Conclusions

The two approaches of periodontal regeneration, Guided tissue regeneration (GTR) and the application of enamel matrix derivatives (EMD), both in conjunctions of bovine bone mineral particles, achieve comparable clinical outcome.

Successful regenerative approach treatment can be achieved in a predictable manner in aggressive periodontitis patients. The key seems to be the meticulous treatment mode, for both techniques followed by a strict supportive periodontal maintenance.

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