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A randomized clinical multicentre trial comparing enamel matrix derivative and membrane treatment of buccal class II furcation involvement in mandibular molars. Part III: patient factors and treatment outcome

Thomas Hoffmann[1], Steffen Richter[1], Joerg Meyle[2], Jose R. Gonzales[2], Bernd Heinz[3], Mehrdad Arjomand[3], Anton Sculean[4], Elmar Reich[5], Karin Jepsen[3], Søren Jepsen[6] and Rolf-Hasso Boedeker[7]

[1]Department of Conservative Dentistry, University of Technology, Dresden, Germany; [2]Department of Periodontology, University of Giessen, Giessen, Germany; [3]Private Practice, Hamburg, Germany; [4]Department of Periodontology, University of Nijmegen, Nijmegen, The Netherlands; [5]Private Practice, Biberach, Germany; [6]Department of Periodontology, Operative and Preventive Dentistry, University of Bonn, Bonn, Germany; [7]Working Group of Medical Statistics, Institute of Medical Informatics, University of Giessen, Giessen, Germany

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Abstract

Objectives: Evaluation of effects of patient factors on the outcome of regenerative treatment of buccal mandibular class II furcation defects.

Material and Methods: Fifty-one patients were recruited. In the intention-to-treat population 21 patients were allocated into the sequence left treatment with enamel matrix protein derivative (EMD) and right guided tissue regeneration (GTR) and 27 in the sequence left GTR and right EMD. Evaluated patient factors were: smoking, age, gender, hypertension and oral hygiene status. Outcome parameters included change of: (a) horizontal depth of the defect at the deepest point (b) distance from the fornix of the furcation to bone crest of the defect, (c) distance from stent to the bottom of the defect, (d) pocket depth and (e) attachment level at the middle of the furcation.

Results: In patients 54 years of age and older, in males, in non-smokers and in patients with ''poor'' hygiene EMD-treated sites showed a significant higher mean reduction of the parameters d (age), b (gender, hygiene) a (smoking, hygiene) when compared with sites treated with GTR.

Conclusions: These data provided an indication of a possible effect of patient factors on the outcome of regenerative treatment of buccal mandibular class II furcation defects.

Key words: enamel matrix derivative; guided tissue regeneration; mandibular class II furcation defects; patient factors; periodontal regeneration; treatment outcome

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Since the introduction of guided tissue regeneration (GTR) in regenerative periodontal therapy (Nyman et al. 1982, Gottlow et al. 1984) numerous histological and clinical studies have been performed in order to evaluate this treatment approach (for a review, see Machtei & Schallhorn 1995, Evans et al. 1997, Cortellini & Tonetti 2000, Sanz & Giovannoli 2000, Jepsen et al. 2002, Lindhe & Palmer 2002).

During the past years guidelines regarding the design of these studies have been drawn up (Caton 1997, Cooley & Castellion 1997, Koch & Paquette 1997, Levine & Dennison 1997, Machtei 1997, Milgrom et al. 1997, Tu et al. 2006).

Recent studies have indicated that the outcome of GTR therapy is strongly dependent upon various factors such as: (i) bacterial contamination, (ii) innate wound-healing potential, (iii) local site characteristics and (iv) surgical procedure (Kornman & Robertson 2000). Additionally, Cortellini & Tonetti (2000) described factors affecting treatment outcome that were derived from studies in which multivariate approaches had been employed (Tonetti et al. 1993, 1995, 1996, Machtei et al. 1994). The most important among these factors are: (i) patient-associated, (ii) defect-associated, (iii) surgical procedure-associated and (iv) healing period-associated ones.

Furthermore, it was shown in epidemiologic as well as clinical studies that in addition to the known risk factors for periodontitis like smoking and diabetes mellitus there are possible further associations between periodontitis and age (Norderyd et al. 1999, Albandar 2002, Nunn 2003), gender (Grossi et al. 1994, 1995, Hyman & Reid 2003), hypertension (Angeli et al. 2003) and genetics (Loos et al. 2005) which might also have an influence on periodontal healing.

Recent systematic reviews of studies in regenerative periodontal surgery also concluded that there is a need for future investigations to identify factors associated with more predictable benefits (Jepsen et al. 2002, Needleman et al. 2002, Trombelli et al. 2002).

Most of the available studies on the use of an enamel matrix protein derivative (EMD) evaluated the outcome in the therapy of intra-bony defects (Heijl et al. 1997, Pontoriero et al. 1999, Sculean et al. 1999, 2001, Tonetti et al. 2002) and, until now, there is only very limited evidence on the healing of furcation type defects with (EMD). Very recently, we have demonstrated that regenerative periodontal surgery with (EMD) may also lead to significant improvements in mandibular class II furcation defects (Jepsen et al. 2004, Meyle et al. 2004).

The aim of the present investigation was to evaluate, based on the reported data (Jepsen et al. 2004, Meyle et al. 2004), some possible effects of patient factors on the outcomes following regenerative treatment of mandibular class II furcations.

Materials and Methods

The study protocol (design, randomization, primary and secondary parameters, time schedule, surgical procedure, follow-up, etc.) was previously described (Jepsen et al. 2004).

Briefly, the objective of this superiority trial was to prove if the healing of buccal degree II furcation defects in mandibular molars following regenerative periodontal surgery with EMD (Emdogain®, BIORA AB, Malmö, Sweden) resulted in better clinical outcomes than GTR treatment with a bioresorbable membrane (Resolut®, Gore, Flagstaff, AZ, USA). Having met the criteria for inclusion and having agreed to the informed consent, the patients were randomly allocated to the two sequences. For each patient the study started with surgery on the left side, was continued with surgery on the right side, and was finished after several follow-ups with a re-entry at 14 months post-surgery. The most important inclusion criterion was the presence of a buccal class II furcation in both lower first or second molars. Teeth displaying class III or lingual class II furcation involvements as diagnosed during surgery were excluded from the study.

The primary outcome variable was the change in horizontal depth of the furcation defect measured from the deepest point during surgery and re-entry. Secondary parameters included changes in all the anatomical measurements of hard tissue boundaries in the furcation defect and the clinical parameters, level of gingival margin, pocket depth, bleeding, attachment level, bone sounding and classification of buccal and lingual furcation defect. All variables measured during surgery or re-entry at 14 months post-surgery, respectively, were measured twice.

In order to describe oral hygiene full-mouth plaque index and site plaque were assessed at 8–12 weeks, 3, 6, 8 and 14 months post-surgery. Possible adverse reactions were recorded by open questioning of the patient during the study.

Data were double entered in two databases. Having checked quality and validity of the data and having closed the database the analysis populations were determined. As the study was conducted in a split mouth/carry-over design no site-treatment interaction is the general assumption. The analysis of the primary parameter was done in a confirmatory manner with a level of significance $\alpha = 0.05$. All the other observed or measured parameters were analysed in an exploratory or descriptive manner. For the analysis of the primary variable with the intention-to-treat population, if a value was missing then the last post-treatment value before the missing value was used. As the data did not provide sufficient evidence to the assumption of normal distribution non-parametric tests were used.

Description of population and analysis sets

A total of 51 patients were recruited. Because of fulfilling one of the major exclusion criteria before or during second surgery three patients had to be excluded from the intention-to-treat population. Furthermore, three patients had to be excluded from the per protocol population because of relevant protocol violations. In the intention-to-treat population 21 patients were allocated into the sequence left Emdogain® and right Resolut® (LE–RM) and 27 in the sequence left Resolut® and right Emdogain® (LM–RE). Twenty two patients were female and 26 male. Ten patients were active smokers (>20 cigarettes/day). At first for the parameters measured before or during surgery on the left side the homogeneity of both sequences was tested. No indication for the rejection of the assumption of homogeneity could be found.

The following patient factors were studied with regard to their possible influence of the treatment outcome (Table 1):

- smoking
- age
- gender
- hypertension
- oral hygiene status

The influencing factors smoking and high blood pressure were assessed on the basis of the baseline questionnaire and were divided into smokers (>20 cigarettes/day) *versus* non-smokers, hypertension *versus* no hypertension. The age groups were divided into

Table 1. Classification of influencing factors

Influencing factor	Classification
Smoking	Yes (smoker) no (non-smoker)
Age	$\leq$ 54 />54 years
Gender	Female/male
Hypertension	Yes/no
Full-mouth plaque score	$\leq$ 15% versus >15%
Oral hygiene (longitudinally)	Good/poor (less or more than two of five possible sites with plaque on three or more investigation times)

$\leq$ 54 and >54 years of age according to the median value of the age of all patients.

The classification of personal oral hygiene was based on the full-mouth plaque score at re-entry. The critical value to distinguish between the two groups was a full-mouth plaque score $\leq$ 15% or >15%.

The second way of classification was based on longitudinal assessments of plaque at the buccal aspect of the mandibular molars. If one patient exhibited on three or more appointments at two or more of the five possible sites (mesiobuccal, mesial root, midfurcation, distal root, distobuccal) the presence of plaque, the patient was classified as having a ''poor'' oral hygiene (Table 1).

The parameters that described treatment outcome (outcome parameters) were:

- change of horizontal depth of the defect at the deepest point
- change of distance from the fornix of the furcation to bone crest of the defect
- change of distance stent to the bottom of the defect
- change of pocket depth at the middle of the furcation
- change of attachment level at the middle of the furcation (Jepsen et al. 2004, Meyle et al. 2004)

Statistical analysis

For the present investigations explorative data analyses including subgroup analyses were applied. Investigating the subgroups methods for analysing the split-mouth/cross-over design were used. We computed effect estimates for treatment and corresponding 95% confidence intervals. Furthermore the corresponding *p*-values were computed using the adequate tests. No adjustments were made for multiple comparisons, as all tests were explorative and the results have to be interpreted in this manner.

In order to be able to interpret the results the following assumptions had to be checked:

1. Existence of homogeneity of the distributions of the possible influencing factors between the two sequences.
2. Existence of associations between the influencing factors.
3. Existence of homogeneity of the distributions of the baseline measurements separated by the influencing factors, treatment and sequences.

In order to check for homogeneity of the distribution of the patient factors between the different sequences at baseline, Fisher's exact test was used.

Because of testing different patient factors that also could show associations amongst themselves the second step included the screening for these possible associations also using Fisher's exact test.

In a third step the comparability of the distribution of the outcome parameters at baseline separated by the influencing factors, treatment modality and sequence was demonstrated.

Having checked all the necessary assumptions the fourth step was directed to the detection of associations between treatment outcome and influencing factors. Therefore, for all patients of the intention-to-treat population parameters describing the distribution of changes between baseline and re-entry of the outcome parameters separated by sequence and treatment and patient factors were calculated. In order to demonstrate possible differences between the groups defined by the expressions of the influencing factors the *p*-value, the Hodges–Lehmann estimator and the corresponding 95% confidence interval were computed.

Results

As demonstrated in Table 2a, b there was no indication that the distribution of the patient factors smoking, age, gender, hypertension and oral hygiene was any different in the two sequences (left EMD–right GTR and left GTR–right EMD).

Therefore, a structural similarity at baseline could be assumed.

The distribution of smoking in females was comparable with that in males. The same holds true for the association between smoking and hypertension.

As expected the amount of patients suffering from hypertension was higher in the older age group (>54 years) compared with that found in the younger one. The distribution of gender in the two age groups was comparable and there was no association between hypertension and gender.

For all patient factors in the single sequences as well as in both sequences combined from the clinical and from the statistical point of view the baseline data of the outcome parameters was regarded as comparable. Thus, no differences which had to be taken into account during the further comparisons were found at baseline.

The tables with the results of testing the influence of each factor for each outcome parameter will only be presented in an exemplary fashion (e.g. only the results revealing of an influence of the patient factor of interest on the outcome will be presented).

Smoking

Table 3a, b illustrate the possible influence of smoking on the outcome parameter ''horizontal depth of defect at the deepest point''. As shown in Table 3a, in non-smokers the EMD-treated sites exhibited a higher median reduction of horizontal depth of defect at the deepest point compared with membrane-treated sites (2.75 *versus* 1.75). The 95% confidence interval and the computed *p*-value (Table 3b) are an indication of superiority of EMD over GTR in the subgroup of the non-smokers. This tendency could not be shown in the group of the smokers, possibly owing to the small sample size.

Table 2a. Distribution of the influencing factors smoking, age, gender, hypertension in the two sequences left Emdogain® (LE)–right membrane (RM) and left membrane (LM)–right Emdogain® (RE)

	Smoking			Age (years)			Gender			Hypertension		
	no	yes	total	⩽54	>54	total	female	male	total	no	yes	total
LE–RM	15	6	21	12	9	21	12	9	21	17	4	21
%	71.43	28.57		57.14	42.86		57.14	42.86		80.95	19.05	
LM–RE	23	4	27	13	14	27	10	17	27	23	4	27
%	85.19	14.81		48.15	51.85		37.04	62.96		85.19	14.81	
Both	38	10	48	25	23	48	22	26	48	40	8	48
%	79.17	20.83	100.00	52.08	47.92	100.00	45.83	54.17	100.00	83.33	16.67	100.00
Fisher's exact test		0.30			0.57			0.24			0.72	

Table 2b. Distribution of the influencing factors full-mouth plaque index and oral hygiene in the two sequences left Emdogain® (LE)–right membrane (RM) and left membrane (LM)–right Emdogain® (RE)

	Full-mouth plaque index			Oral hygiene		
	⩽ 15%	>15%	total	good	poor	total
LE–RM	12	8	20	12	7	19
%	60.00	40.00		63.16	36.84	
LM–RE	13	14	27	12	15	27
%	48.15	51.85		44.44	55.56	
Both	25	22	47	24	22	46
%	53.19	46.81	100.00	52.17	47.83	100.00
Fisher's exact test		0.56			0.24	

Table 3a. Distribution of the change (surgery–re-entry) of secondary parameter measuring hard tissue boundaries separated by sequence and treatment and smoking habits, intention-to-treat population; horizontal depth of defect at the deepest point

Sequence	Tobacco smoking	*n*	Treatment					
			Emdogain®			membrane		
			minimum	medium	maximum	minimum	medium	maximum
LE–RM	Yes	6	− 1.00	0.88	3.50	0.00	0.88	2.00
	No	15	− 1.25	2.00	8.75	− 0.50	2.25	5.00
LM–RE	Yes	4	0.00	2.75	4.75	0.00	2.75	4.75
	No	23	− 1.25	3.00	5.00	− 0.50	1.75	4.75
Both	Yes	10	− 1.00	1.50	4.75	0.00	1.25	4.75
	No	38	− 1.25	2.75	8.75	− 0.50	1.75	5.00

LE, left Emdogain®; RE, right Emdogain®; RM, right membrane; LM, left membrane.

Table 3b. Estimators of the differences of the changes of ''horizontal depth of defect at the deepest point'' under treatment with Emdogain® and Membrane (intention-to-treat population) separated for smokers and non-smokers

Variable	Tobacco smoking	*n*	Hodges–Lehmann estimator	95% confidence interval	*p*-value*
Horizontal depth of defect at the deepest point	Yes	10	− 0.438	[− 1.625; 2.375]	0.505
	No	38	0.775	[0.000; 1.400]	0.043

*Wilcoxon's two sample test; the *p*-value is a measure of the distance from the observed statistic to the value of the parameter specified by the assumption that both samples were drawn from the same population. That means the greater the *p*-value, the more likely is the event that both therapies have the same effect.

Age

In the age group >54 years ($n = 22$) a higher reduction of pocket depth at the middle of the furcation following treatment with EMD (0.37 mm) compared with membrane treatment was observed, $p = 0.045$ (Table 4a, b). In the subgroup of the younger patients (⩽ 54 years, $n = 25$) this tendency could not be observed.

Gender

Tables 5a, b demonstrate that in male patients ($n = 24$) EMD treatment resulted in a higher reduction (0.69 mm) of the distance from the fornix of the furcation to the bone crest of the defect than membrane placement ($p = 0.031$). This tendency could not be shown in the subgroup of the female patients ($n = 21$).

Oral Hygiene

When evaluating the influence of oral hygiene (good/poor, see Table 1), in patients with ''poor'' oral hygiene a statistically significant higher reduction of the parameters: ''distance from the fornix of the furcation to the bone crest of the defect'' ($n = 22$, $p = 0.040$) and ''horizontal depth of defect at the deepest point'' ($n = 22$, $p = 0.040$) was found for teeth treated with EMD compared with teeth treated with membrane therapy (Tables 6a, b and 7a, b). This tendency could not be observed in patients with ''good'' oral hygiene for both parameters ($n = 22$ and 24).

Table 4a. Distribution of the change (surgery–14 months post) of the secondary parameters (clinical parameters) separated by sequence and treatment and age, intention-to-treat population; Pocket depth at the middle of the furcation

Sequence	Age (years)	*n*	Treatment					
			Emdogain®			membrane		
			minimum	medium	maximum	minimum	medium	maximum
LE–RM	>54	8	− 0.25	0.13	1.50	0.00	0.50	1.50
	≤ 54	12	− 0.50	1.00	3.50	− 3.00	1.00	7.25
LM–RE	>54	14	− 0.25	0.63	4.25	− 1.00	0.00	1.75
	≤ 54	13	− 1.00	0.00	1.75	− 1.25	0.50	2.00
Both	>54	22	− 0.25	0.50	4.25	− 1.00	0.00	1.75
	≤ 54	25	− 1.00	0.50	3.50	− 3.00	1.00	7.25

LE, left Emdogain®; RE, right Emdogain®; RM, right membrane; LM, left membrane.

Table 4b. Estimators of the differences of the changes of ''pocket depth at the middle of the furcation'' under treatment with Emdogain® and Membrane (intention-to-treat population) separated by the two age classes ⩽54 and >54

Variable	Age	*n*	Hodges–Lehmann estimator	95% confidence interval	*p*-value*
Pocket depth, furcation middle	>54	22	0.375	[0.000; 1.000]	0.045
	≤ 54	25	− 0.250	[− 0.875; 0.500]	0.564

*Wilcoxon's two sample test; the *p*-value is a measure of the distance from the observed statistic to the value of the parameter specified by the assumption that both samples were drawn from the same population. That means the greater the *p*-value, the more likely is the event that both therapies have the same effect.

Table 5a. Distribution of the change (surgery–re-entry) of secondary parameter measuring hard tissue boundaries separated by sequence and treatment and gender; intention-to-treat population; distance from the fornix of the furcation to bone crest of the defect

Sequence	Gender	*n*	Treatment					
			Emdogain®			membrane		
			minimum	medium	maximum	minimum	medium	maximum
LE–RM	Male	8	− 0.50	0.75	2.50	− 0.25	0.63	2.75
	Female	11	− 1.00	0.20	3.00	− 1.75	0.25	3.50
LM–RE	Male	16	− 0.50	0.88	4.00	− 1.00	0.00	2.75
	Female	10	− 1.50	0.38	1.00	− 1.00	0.00	1.00
Both	Male	24	− 0.50	0.88	4.00	− 1.00	0.25	2.75
	Female	21	− 1.50	0.25	3.00	− 1.75	0.25	3.50

LE, left Emdogain®; RE, right Emdogain®; RM, right membrane; LM, left membrane.

Table 5b. Estimators of the differences of the changes of ''distance from the fornix of the furcation to bone crest of the defect'' under treatment with Emdogain® and Membrane (intention-to-treat population) separated by male and female patients

Variable	Gender	*n*	Hodges–Lehmann estimator	95% confidence interval	*p*-value*
Fornix to bone crest of defect	Male	24	0.688	[0.125; 1.125]	0.031
	Female	21	− 0.125	[− 0.750; 0.375]	0.454

*Wilcoxon's two sample test; the *p*-value is a measure of the distance from the observed statistic to the value of the parameter specified by the assumption that both samples were drawn from the same population. That means the greater the *p*-value, the more likely is the event that both therapies have the same effect.

Regarding all other parameters and patient factors no significant associations could be detected.

Discussion

The main clinical endpoint of any given therapy to treat furcation lesions is the full closure of the furcation, or, if this aim can not be attained, the conversion of a deep into a shallow lesion (Sanz & Giovannoli 2000). However, the predictability of these treatment goals is influenced by several factors. Although not all factors have been yet elucidated they include patient and defect selection, treatment techniques and others (Cortellini & Tonetti 2000, Kornman & Robertson 2000, Sanz & Giovannoli 2000). Thus, there is a need to better understand factors and conditions which may have an influence upon treatment outcome (Lindhe & Palmer 2002).

Consequently, the present analyses have been performed in order to further clarify some of these issues. An important aspect of the present results is that the analyses were performed in relation to treatment modality (i.e., EMD, Membrane). In this way, certain conclusions for these specific therapies were drawn.

Although the overall number of treated furcations was three times higher as in most other studies (for a review, see Sanz & Giovannoli 2000) – except for a multicentre study of Garrett et al. (1997) who compared the treatment outcome of resorbable and non-resorbable membranes in F II defects in both mandibular and maxillary molars – the main problem of these analyses was the relatively low number of cases in the subgroups which had to be divided into the two sequences for these analyses. As these subgroup analyses were not planned in the original study protocol they were performed in an explorative manner.

The weak association between higher age and increase of hypertension found in the present study is in accordance with earlier results from various studies on risk assessment evaluating the association between periodontitis and cardiovascular disease (for a review see DeStefano et al. 1993, Genco 1998, Beck et al. 2000, Kinane & Chestnutt 2000, Kinane & Lowe 2000).

Analytic epidemiological studies (Bergström et al. 2000, Albandar 2002) as well as clinical investigations (Apatzidou et al. 2005) have provided evi-

Table 6a. Distribution of the change (surgery–re-entry) of secondary parameter measuring hard tissue boundaries separated by sequence and treatment and oral hygiene, intention-to-treat population; distance from the fornix of the furcation to bone crest of the defect

Sequence	Oral hygiene	*n*	Treatment					
			Emdogain®			membrane		
			minimum	medium	maximum	minimum	medium	maximum
LE–RM	Good	11	− 1.00	0.20	2.50	− 1.25	0.75	2.75
	Poor	7	− 0.50	2.00	3.00	− 1.75	0.00	3.50
LM–RE	Good	11	− 1.50	0.50	2.50	− 1.00	0.00	1.25
	Poor	15	− 0.50	0.75	4.00	− 0.75	0.50	2.75
Both	Good	22	− 1.50	0.38	2.50	− 1.25	0.13	2.75
	Poor	22	− 0.50	1.00	4.00	− 1.75	0.25	3.50

LE, left Emdogain®; RE, right Emdogain®; RM, right membrane; LM, left membrane.

Table 6b. Estimators of the differences of the changes of ''distance from the fornix of the furcation to bone crest of the defect'' under treatment with Emdogain® and membrane (intention-to-treat population) separated by patients with good and poor oral hygiene

Variable	Oral hygiene	*n*	Hodges–Lehmann estimator	95% confidence interval	*p*-value*
Fornix to bone crest of defect	Good	22	0.000	[− 0.625; 0.500]	0.910
	Poor	22	0.750	[0.000; 1.625]	0.040

*Wilcoxon's two sample test; the *p*-value is a measure of the distance from the observed statistic to the value of the parameter specified by the assumption that both samples were drawn from the same population. That means the greater the *p*-value, the more likely is the event that both therapies have the same effect.

Table 7a. Distribution of the change (surgery–re-entry) of secondary parameter measuring hard tissue boundaries separated by sequence and treatment and oral hygiene, intention-to-treat population; horizontal depth of defect at the deepest point

Sequence	Oral hygiene	*n*	Treatment					
			Emdogain®			membrane		
			minimum	medium	maxium	minimum	medium	maximum
LE–RM	Good	12	− 1.25	1.38	4.30	0.00	1.88	3.50
	Poor	7	1.25	2.00	8.75	− 0.50	1.00	5.00
LM–RE	Good	12	0.00	2.75	5.00	0.00	1.75	4.25
	Poor	15	− 1.25	3.00	5.00	− 0.50	1.75	4.75
Both	Good	24	− 1.25	2.25	5.00	0.00	1.75	4.25
	Poor	22	− 1.25	3.00	8.75	− 0.50	1.63	5.00

LE, left Emdogain®; RE, right Emdogain®; RM, right membrane; LM, left membrane.

Table 7b. Estimators of the differences of the changes of ''horizontal depth of defect at the deepest point'' under treatment with Emdogain® and Membrane (intention-to-treat population) separated by patients with good and poor oral hygiene

Variable	Oral hygiene	*n*	Hodges–Lehmann estimator	95% confidence interval	*p*-value*
Horizontal depth of defect at the deepest point	Good	24	0.125	[− 0.500; 0.900]	0.637
	Poor	22	1.250	[0.000; 2.250]	0.040

*Wilcoxon's two sample test; the *p*-value is a measure of the distance from the observed statistic to the value of the parameter specified by the assumption that both samples were drawn from the same population. That means the greater the *p*-value, the more likely is the event that both therapies have the same effect.

dence that smoking is one of the important risk factors for periodontitis. Generally, assessment of risk shows that smoking is associated with a two- to seven-fold increase in risk for periodontitis compared with non-smokers (Bergström & Preber 1994, Grossi et al. 1994, 1995, Gelskey et al. 1998, Tomar & Asma 2000).

In addition smoking interferes with wound healing in general (Frick & Seals 1994, Chang et al. 1996, Kwiatkowski et al. 1996) and influences periodontal healing and regeneration (Tonetti et al. 1993, 1995, 1996, Machtei et al. 1994, Rosenberg & Cutler 1994, Preshaw et al. 2005). As Rosenberg & Cutler (1994) demonstrated, 80% out of the 42% failure rate during a 4-year time period of GTR procedures in class II furcations were in patients who smoked at least 10 cigarettes/day for 5 years. Comparable results were also reported by Tonetti et al. (1995) for intra-bony defects and by Bowers et al. (2003) for furcation defects. Both studies have shown that at 1 year after regenerative treatment smokers displayed significantly less favourable gain in probing attachment level compared with non-smokers.

Our data indicate that EMD treatment in non-smokers may result in higher reduction of horizontal depth of the furcation defect than membrane placement. Previous studies reported no statistically significant association between age or gender and the outcome of regenerative periodontal therapy (Machtei et al. 1994, Rosenberg & Cutler 1994, Luepke et al. 1997). Our analyses indicate that in male patients EMD may yield higher reduction of the distance from the fornix of the furcation to bone crest of the defect compared with membrane placement. This tendency could not be observed for female patients. Furthermore, in the higher age group (>54 years) treatment with EMD resulted in more favourable results than membranes. Although it is difficult to find a biologic explanation for these findings, it may be speculated that in non-smokers and in older patients, treatment with EMD, aiming to promote differentiation and proliferation of phenotypic cells, might lead to certain additional benefits compared with a more mechanically based therapy such as membrane therapy. However, further studies are needed in order to further validate the present observations.

The benefits of plaque control on the response to periodontal therapy are well

documented in the literature (Lindhe et al. 1984, Cobb 1996). In a 4-year study it has been shown, that the mean gain of 4.1 mm of clinical attachment level 1 year after GTR under strict plaque control was stable for an additional 3 years in 15 patients. In the other 8 patients who received sporadic plaque control only, a mean gain of 2.8 mm of the first year was lost in the next 3 years (Cortellini et al. 1994). Falk et al. (1997) explained 47% of the variability in clinical attachment level by defect characteristics, early membrane exposure and the presence of plaque at treated sites. Machtei et al. (1994) observed that optimal treatment outcome in class II furcations was associated with good oral hygiene and Hugoson et al. (1995) noted that unresponsive class II furcations were associated with high plaque levels.

An interesting aspect of the present results was the finding that in the group of ''poor'' oral hygiene EMD treatment resulted in a higher reduction of both parameters: distance from the fornix of the furcation to bone crest of the defect and horizontal depth of defect at deepest point compared with membrane therapy. Although in general, all patients participating in this study displayed a good level of plaque control, EMD treatment appeared to be influenced by plaque accumulation to a lesser degree than membrane treatment. One possible explanation for this finding may be the positive effect of EMD on the early wound healing events. Data from ''in vitro'' studies have provided evidence that periodontal ligament fibroblasts treated with EMD displayed an increased intra-cellular cAMP concentration and autocrine releasing of TGF-1β, IL-6 and PDGF in comparison with the control group (without addition of EMD) (Lyngstadaas et al. 2001). These results were also corroborated by others indicating that EMD promotes the release of autocrine growth factors from desmodontal fibroblasts and enhances matrix synthesis in gingival fibroblasts (Hoang et al. 2000, van der Pauw et al. 2000, Haase & Bartold 2001, Lyngstadaas et al. 2001, Keila et al. 2004).

Recent data have also suggested that EMD possesses certain antibacterial effects and may interfere with bacterial adherence (Sculean et al. 2001, Arweiler et al. 2002, Spahr et al. 2002, Newman et al. 2003). It has been shown that EMD inhibits the growth of the periodontal pathogenic bacteria *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis* and *Prevotella intermedia*. Twenty-four hours following the application of EMD no viable colonies of these pathogenic bacteria could be observed (Spahr et al. 2002). Moreover, EMD demonstrated no negative effect on Gram-positive bacteria (Spahr et al. 2002, Newman et al. 2003). Clinically, the positive effect of EMD upon the early wound healing is supported by the findings of Wennstrom & Lindhe (2002) indicating that topical application of EMD in periodontal pockets in conjunction with non-surgical periodontal therapy enhanced early healing of periodontal soft tissue wounds and was also confirmed in the present study where patients experienced significantly less swelling and pain following EMD therapy in comparison with membrane treatment (Jepsen et al. 2004).

In summary, the present data indicate a slight superiority of regenerative furcation therapy using enamel matrix derivative when compared with membranes in the older age group, in non-smokers, in male patients and patients with poor hygiene.

Furthermore, several markers of patients' status such as the blood biochemical analysis, the body mass index, genetic markers of susceptibility, psychological stress and coping mechanisms might have a possible influence on periodontal disease initiation, progression and response to therapy. As these markers have not been taken into account in our investigations further studies are needed to confirm the observed associations and to screen for additional ones.

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Address:
Thomas Hoffmann
Department of Conservative Dentistry
University of Technology
Dresden
Germany.
E-mail: th.hoffm@rcs.urz.tu-dresden.de

Clinical Relevance

Scientific rationale: Previous investigations have shown the outcome of regenerative periodontal treatment to be dependent on various factors such as patient-, defect- and surgery-associated ones. However, there is no data available on the possible effects of patient factors on the outcome of regenerative treatment of buccal class II furcation involvement in mandibular molars using enamel matrix derivative.

Principal findings: In the present large multi-centre clinical trial EMD treatment demonstrated a tendency of superior clinical outcomes in patients 54 years of age and older, in non-smokers, in male patients and in patients with less perfect oral hygiene when compared with membrane therapy.

Practical implications: The influence of patient factors should be considered in the choice of treatment modality for the regenerative treatment of mandibular furcation defects.