Periodontal Regeneration: A Split-Mouth Controlled Clinically 5-Year Case Study

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Guided tissue regeneration (GTR) with biodegradable polylactide/polyglycolide acid (PLA/PGA) membranes was compared to open curettage and scaling and root planing (SRP) and reevaluated after 6 months and 5 years. Wound healing up to the sixth week postoperatively is considered to be important for the regenerative effect. The purpose of the study was to determine whether GTR is superior to open curettage and SRP. Thirty-six teeth in 20 patients (8 females/12 males) with an average age of 44.6 years (17-64 years) were treated with GTR, applying resorbable PLA/PGA membranes. Either open curettage or SRP was carried out on contralateral teeth. After 2, 4 and 6 weeks, wound healing was assessed. After intraindividual comparison to conventionally treated reference teeth, the difference of the clinical attachment level (ΔCAL), furcation involvement, and PPD was measured 6 months and 5 years postoperatively. The statistical significance was tested with the Mann-Whitney U-test. Disturbed wound healing was only seen after the GTR procedure (8 membrane exposures after 2 weeks, 1 after 4 weeks, none after 6 weeks). After 6 months, ΔCAL measured 1.5 mm (3.9 mm/2.4 mm) in comparison to open curettage and 0.9 mm (3.3 mm/2.3 mm) compared to SRP. Five years after GTR, there was a mean attachment gain of 3.8 mm. Our study shows that GTR with resorbable membranes is superior to open curettage and SRP in the treatment of vertical bone defects.

Key words: resorbable PLA/PGA membranes, furcation involvement, vertical bony defects, guided tissue regeneration, GTR

INTRODUCTION AND AIMS

Periodontal regenerative treatment aims at a complete morphological re-establishment of the former architecture of all kinds of tissues that have been lost due to periodontal inflammation. Since Nyman et al. (1982) demonstrated the principle of guided tissue regeneration (GTR) to be successful in humans by employing a millipore filter membrane, non-absorbable expanded polytetrafluorethylene (e-PTFE) was first used, and later, absorbable materials were introduced in this kind of treatment.

The polylactide-polyglycolide membrane (PLA-PGA) (Resolut®) resorbable barrier undergoes. After hydrolytic cleavage of the ester into glycol and lactic acid afterwards, the material is further degraded into CO_2 and H_2O in the citric acid cycle, thus not impairing the periodontal wound (Hutmacher 1995, 1996; Kronenthal, 1975).

Up to now, there have been relatively few studies on the long-term outcome of absorbable membranes in GTR. Eickholz et al. (2001) applied clinical and standardized radiographic parameters in nine patients with Class II furcation involvement. After five years in this prospective randomized split-mouth study that compared non-absorbable e-PTFE membranes to absorbable polyglactine-910 membranes, no statistical differences were found. In an 18-month longitudinal case-control study, Grimm et al. (2000) showed in ten patients with three furcation involvements and seven intrabony defects that the presence of sulfate-reducing bacteria within the periodontal pocket before GTR is a negative predictor for early wound healing after the application of PLA/PGA membranes but has no influence on the long-term outcome.

In a randomized split-mouth study, Sculean et al. (2001) demonstrated the stability of clinical attachment gains achieved by the application of absorbable membranes in comparison to an enamel matrix derivative in 12 patients after four years.

With a study design analogous to the one of Eickholz et al. (2001) described above, Kim et al. (2002) observed stability in 14 of 16 cases (in 8 of the original 12 patients) after 5 years where non-absorbable e-PTFE membranes vs absorbable polyglactin-910-membranes were used in periodontal intrabony defects; no statistically significant differences were found based on the two different materials applied.

In our split-mouth longitudinal clinical controlled case study, periodontal regeneration after GTR with PLA/PGA membranes was compared to open flap debridement (OFD) and scaling and root planning (SRP), focussing on postoperative wound healing at six weeks, six months, and five years. All patients took part in our supportive periodontal treatment program – including professional tooth cleaning – every three months.

STUDY DESIGN AND RESULTS

In 20 patients (8 women, 12 men) with an average age of 44.6 years (ranging from 17 to 64 years), 36 teeth were treated with GTR applying PLA/PGA membranes. According to the medical indication, contralateral teeth were treated either with OFD or SRP. Randomization was not possible. In six individuals, 16 GTR treated teeth with vertical bone defects (PPD_{begin} = 7.4 mm ± 1.5 mm / AL_{begin} = 8.8 mm ± 1.4 mm) were compared to OFD performed on a contralateral tooth (PPD_{begin} = 5.8 mm ± 1.6 mm / AL_{begin} =6.3 mm ± 1.4 mm), and in 14 individuals, 20 GTR-treated teeth with vertical bone defects (PPDbegin 6.7 mm ± 1.8 mm / AL_{begin} = 8.4 mm ± 2.1 mm) were compared to a SRP-treated contralateral tooth (PPDbegin =4.9 mm ± 1.4 mm / AL_{begin} = 5.9 mm ± 1.6 mm).

Two to three wall defects were found intraoperatively, the presence of which had been assumed based on preoperative radiographic and clinical evaluation. Six anterior teeth (5 maxillary), 9 premolars (4 maxillary), and 21 molars (11 maxillary) amounted to 36 GTR treated teeth. Furcation involvement was treated in 11 cases. Class I was seen in 6 teeth (5 maxillary molars, 1 mandibular molar), Class II in 4 teeth (two first and two second maxillary molars), and Class III in 1 tooth (first mandibular molar).

After 5 years, 20 GTR-treated teeth in 12 patients could be re-evaluated. In 4 individuals, 9 GTR-treated teeth were compared to OFD, and in 8 patients, 11 GTR-treated teeth were compared to SRP. It was possible to re-evaluate furcation involvement in 5 patients (Class I: two first maxillary molars and one second maxillary molar; Class II: one first maxillary molar; Class III: one first mandibular molar).

The patients taking part in the study were informed about alternative treatment possibilities and gave informed consent.

Operative Procedure

All patients underwent initial periodontal treatment and SRP. After rinsing with a 0.2% chlorhexidine digluconate rinse and local anaesthesia, the GTR operative procedure was started with full-thickness flap raising. An intrasulcular incision was made to preserve the vertical flap dimension, while the interdental papillae were preserved as far as possible. In order to achieve good visibility into the defect and mobility of the flap, vertical incisions were made. To allow final coronal positioning of the flap without tension, a releasing incision was placed into the periosteum apical to the mucogingival junction. Vertical incisions and the periosteal releasing incision were not performed as part of the OFD procedure.

From the inner side of the flap, granulation tissue and apically-proliferated epithelium were excised with the gingival scissors. All the granulation tissue within the intrabony defect was removed, and scaling and root planing was carried out using the reduced Gracey curette set. The operation field was irrigated with 0.9% sodium chloride solution to remove loosened detritus consisting of pieces of granulation tissue, calculus, and infected cementum, and to keep the tissue humid and vital.

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According to the morphology of the defect, the shape of the membrane was chosen and finally configured under sterile conditions so that the membrane completely covered the defect, exceeding the defect margin by a minimum of 2-3 mm. For fixing the membrane, a wrap around the tooth suture with absorbable polyglycolic acid suture material with polycaprolate coating (Dexon II®) was utilized. To achieve primary closure, oral and vestibular flap compartments were rejoined using non-absorbable e-PTFE interdental, vertical or horizontal reinforced mattress sutures, modified according to Laurell.

Neither periodontal dressing nor antibiotics were prescribed, but instead a non-steroidal anti-inflammatory drug (Ibuprofen 400®) was administered for analgesia and swelling prophylaxis. A 0.2% chlorhexidine digluconate rinse was prescribed to be used twice a day for 1 minute to reduce bacteria. The non-absorbable sutures were removed after 10 to 12 days. Professional tooth cleaning and wound control was performed every two weeks within the first two months postoperatively. Then monthly controls followed until the sixth month. At this point, the recall interval changed to every 3 months.

Method of Evaluation

Before surgery, pocket probing depth (PPD), recession (R) and the clinical attachment level (CAL) were measured using the PCP11-probe; further, furcation involvement was assessed using the Nabers furcation probe.

Six weeks postoperatively, wound healing was evaluated according to the following scale: "very good" (no signs of inflammation, no recession), "undisturbed" (moderate signs of inflammation, e.g., slight redness, slight swelling, and a low Class of recession up to 1 mm) and "impaired" (heavy signs of inflammation and gingival recession >1 mm).

An intraindividual comparison not restricted to one jaw was conducted between the control periodontium treated with either SRP or OFD and the vertical bone defect (vBD) treated with GTR. Intraindividually, the changes in PPD and in CAL were calculated after 6 months, and in 12 patients with 20 teeth involved after 5 years. The statistical significance was tested applying the Mann-Whitney U-test ($p<0.05$).

RESULTS

Disturbed wound healing was only seen in GTR procedures. Eight membrane expositions were seen after 2 weeks and one more after 4 weeks. After 6 weeks, the wound healing was evaluated as "very good" in all cases.

In Figure 1, membrane exposition 2, 4, and 6 weeks postoperatively is correlated to the attachment gain after 6 months. In 4 teeth that showed membrane expositions after 2 weeks, an attachment gain of 2-3 mm was seen. In 2 teeth, it was 4-5 mm, and in two further teeth, an increase in the attachment of 6-7 mm was seen. In one case where membrane exposition was seen after 4 weeks, an attachment gain of 2-3 mm after 6 weeks was observed. No membrane exposition was seen 6 weeks postoperatively.

There was a 1.5 mm difference in attachment gain of teeth treated with OFD in comparison to the GTR group, which was calculated from the values of the PLA/PGA group (3.9 mm ±1.1 mm; n=16) and the values of the OFD group (2.4 mm ± 0.9 mm; n = 6). The results were statistically significant ($p<0.01$) (Fig. 2). Compared to SRP (Fig. 3), the difference after 6 months was 0.9 mm, which was derived from the PLA/PGA group with 3.3 mm ± 1 mm (n = 20) and the SRP group with 2.3 mm ±1.2 mm (n = 14) ($p< 0.45$). After 5 years, there was a difference in CAL of 1.3 mm between the PLA/PGA (3.8 mm ± 1.7 mm; n = 9) and the OFD group (2.5 mm ± 1.3 mm; n = 4). This was not statistically significant due to the small sampling number ($p<0.17$) (Fig. 4). Comparing the values of the PLA/PGA group (3.7 mm ± 1.7 mm; n = 11) to SRP group (1.5 mm ± 1.7 mm; n = 8) after 5 years showed a statistically significant difference of 2.2 mm in favour of the PLA/PGA group ($p<0.05$) (Fig. 5).

The average attachment gains 6 months and 5 years postoperatively showed permanence of the attachment level reached where the periodontal regenerative procedure employed consisted of polylactide polyglycolide co-polymer matrix membranes (Fig. 6).

Furcation involvement in one tooth improved from Class III to Class I, in two teeth from Class II to Class I, in two teeth from Class II to Class I, and in five teeth from Class I to Class 0. In one case, furcation involvement remained unchanged. In 45.4% of the cases, a change from Class I to Class 0 was

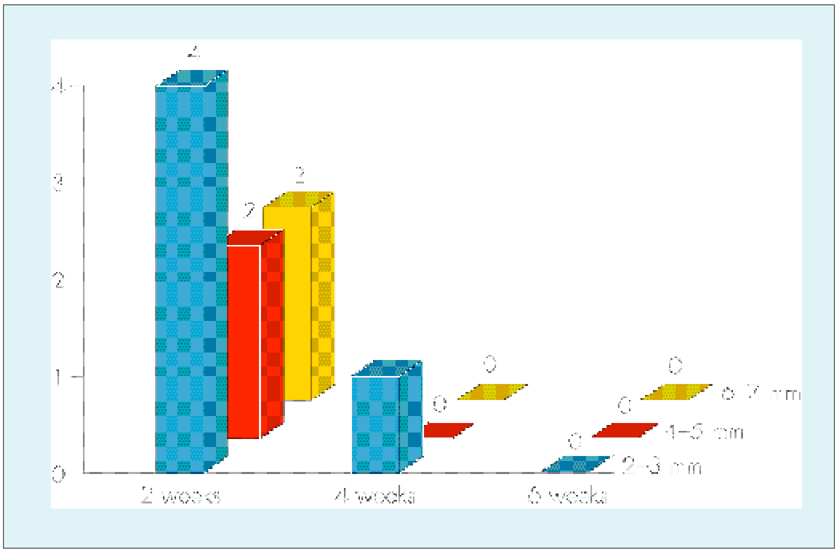

Fig. 1 Six months after GTR with membrane exposition, clinical attachment gains of up to 7mm are achievable.

observed; a change from Class II to Class I and from Class II to Class 0 was seen in 18.2% of the cases, and in 9.1% either no change or an improvement from Class III to Class I was found.
After 5 years, five furcation involvements could be re-evaluated. The furcation that changed from Class III to Class I remained stable. Two teeth improved from Class II to Class 0 and two from Class I to Class 0 (Tab. 1).
After 5 years, the permanence of CAL gains observed after 6 months was re-evaluated: it either remained constant or improved in 12 of 20 cases, a loss of 1 mm was seen in five cases, and one each was observed with a loss of 2, 3, and 5 mm. The tooth with a loss of 5 mm after 5 years had shown a gain of 7 mm after 6 months, despite membrane exposition after 2 weeks (Fig. 7).

DISCUSSION

The results of our longitudinal clinical controlled 5-year case study show that clinical attachment gain can be achieved with the treatment modalities evaluated in this study.
No antibiotics were administered in any of the surgical cases. This was in accord with Minabe et al. (2001), who observed no clinical benefit from the administration of tetracyclines as an adjunct to GTR procedures with collagen membranes. On the other hand, Chang and Yamada (2000) demonstrated a statistically significant gain in bone height ($p<0.05$) and bone surface ($p<0.005$) in experimental bone defects created in a dog model treated with 25% doxycycline-loaded biodegradable membranes. The authors deduced a positive effect of doxycycline on osteogenesis.
The membrane expositions observed in our study after 2 and 4 weeks had not developed negatively at 6 months, contrary to what might have been expected; however, concerning the case with the 5-mm loss after 5 years, membrane exposition after 2 weeks can be regarded as causal. An in-vitro study by Hung et al. (2002) showed lower permeability for *S. mutans* and *A. actinomycetemcomitans* of e-PTFE membranes, but revealed better PDL fibroblast colonization on contaminated collagen type I membranes and glycolide fiber composite membranes in comparison to e-PTFE membranes. De Sanctis et al. (1996) found a 50% reduction of the CAL gain was to be expected if e-PTFE membranes are exposed postoperatively. Urbani et al. (1997) stated that early resorbable membrane exposition under the administration of antibacterial agents does not result in the reduction of expected attachment gains, and thus membrane removal is not necessary. In their comparison of exposed vs non-exposed PLA and polyglactide-910 membranes, Christgau et al. (1997) did not see any statistically significant differences after 6 and12 months, although initially more recession had been documented; further subtraction radiography did not

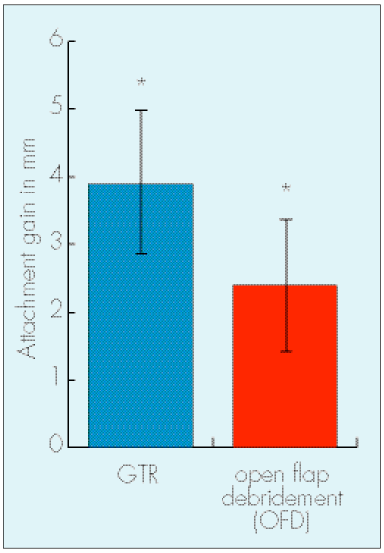

Fig. 2 Difference between the 6-month average attachment gain after GTR with PLA/PGA membranes vs OFD in the control group is 1.5 mm.

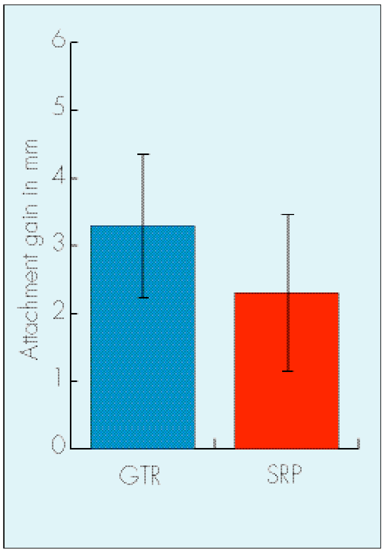

Fig. 3 Difference between the 6-month average attachment gain after GTR with PLA/PGA membranes vs SRP in the control group is 0.9 mm.

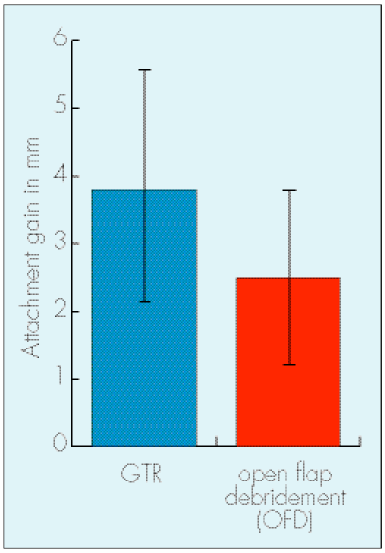

Fig. 4 A tendency indicating an advantage of the GTR procedure with PLA/PGA membranes in comparison to OFD difference 1.3 mm.

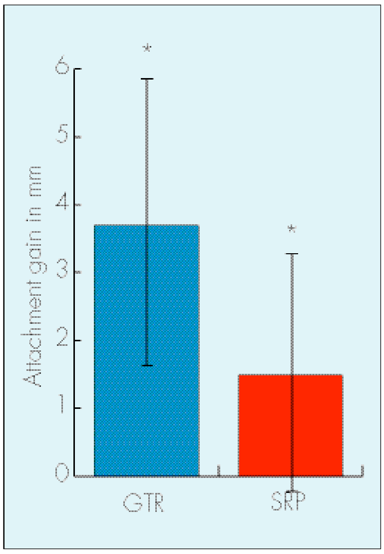

Fig. 5 Difference in clinical attachment gains achieved with GTR employing biodegradable membranes and SRP after 5 years (Δ = 2.3mm, $p < 0,05$).

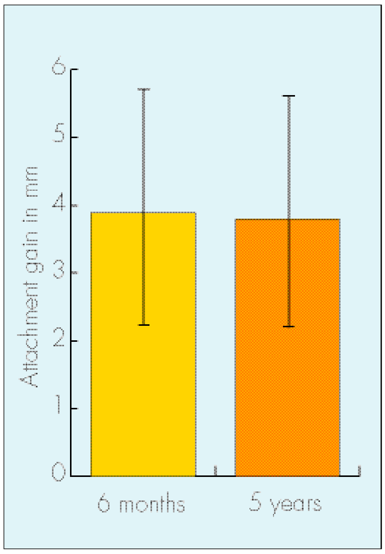

Fig. 6 The diagram shows permanence of the 6-month attachment gains achieved after 5 years when GTR with biodegradable membranes was performed.

reveal any differences concerning bone density and gain. However, bacterial contamination of PLA/PGA membranes leads to membrane degradation within a shorter period of time. Thus, Simion et al. (1997) showed immediate microbial accumulation and bacterial penetration after 3 weeks, with a reduction of thickness of these membranes after 4 to 5 weeks. Membrane degradation is not due to the properties of the saliva itself. This was concluded from a study of Urbani et al. (1997), who found the bacterial load within the saliva to be responsible for the acceleration of membrane degradation after exposure. We assume that the membrane exposure 2 weeks postoperatively was the reason for the 5-mm reduction of attachment level after 5 years from the 7-mm gain that had been observed after 6 months in this case.

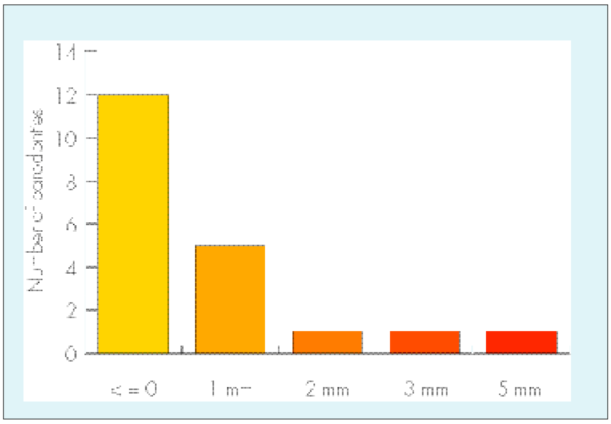

Fig. 7 With early membrane exposure, medium-term attachment gains of up to 7 mm can be observed, but may later drop, as shown at the 5-year re-evaluation of the case in which 5 mm were lost compared to the 6-month value.

In 75% of the cases, uneventful healing was seen in the GTR group treated with PLA/PGA membranes. The reason is thus considered to be the high biocompatibility of this kind of membrane.

According to investigations by Verderio et al. (2001), tissue transglutaminase II (Tgase II), which is found in fibroblasts, osteoblasts, and epithelial cells, plays an important role in the recognition and colonization of artificial polymers. Thus, in vitro experiments of this group revealed higher migration and colonization activity of osteoblasts in contact with polylactide membranes to be correlated to a higher amount of Tgase II within these cells, whereas contact of epithelial cells with this kind of surface led to a reduction in Tgase II and migration and colonization activity in comparison to a glass surface.

In a 24-month prospective study with ten cases of Class II furcation involvement treated with either polylactide citric acid (PLA) or polyglyclide polylactide (PGL) membranes, Buchmann et al. (2001) found that parameter dynamics within the sulcus fluid compared to the status before membrane implantation are dependent on the membrane type used. The amount of myeloperoxidase (MPO), -glucoronidase (,G) and ,-N-acetyl-hexosaminidase (,NAH) was measured in the sulcus fluid, taking this as a polymorph nuclear granulocyte inflammatory answer in reaction to the membrane application. The values decreased earlier in the cases of PLA membranes than they did in the cases of PGA membranes. However, no clinically significant differences were seen. Alpar et al. (2000) detected a moderate in-vitro cytotoxic effect on primary human periodontal ligament fibroblasts and on osteoblast-like cells, which was possibly responsible for a lack of adhesion of these cells to the membrane surface, thus leaving a space to be colonized by quickly proliferating epithelial cells.

A lack of efficacy of GTR employing a biodegradable membrane (Guidor Matrix Barrier®) in comparison to OFD was shown in the results of a study by Radka-Krüger et al. (2000), in which no statistically significant differences were achieved due to the different treatment options applied in this study.

The advantage of biodegradable membranes in GTR consists in making the second-stage surgery superfluous. This of cause especially on the patient side is regarded as a great advantage. In their split-mouth, clinical controlled, longitudinal 30-month study, Christgau et al. found that the results achieved employing polyglactine-910 membranes were equivalent to those obtained with e-PTFE membranes.

Taking the limited number of cases into consideration, the CAL measurements in our study tend – at times statistically significantly – to show that regenerative periodontal therapy employing biodegradable PLA/PGA membranes is superior to SRP and OFD in treating vertical bone defects as monitored longitudinally over a 5-year period. Further, the efficacy of this therapy modality in the treatment of furcation involvement is proven.

Table 1 After GTR with PLA/PGA membranes, furcation involvement can be expected to decrease by one or two classes.

	III to I	II tol	II to 0	I to 0	unchanged
after 6 months	1	2	2	5	1
after 5 years	1	0	2	2	0

CONCLUSIONS

From our results, it can be concluded that the quality of the new attachment is comparable to the attachment before it was lost due to periodontal inflammation. Thus, our study clinically confirms the histological and morphometric results from controlled studies in animals and humans with respect to healing and on effects regeneration achievable with PLA/PGA membranes in GTR.

REFERENCES

Alpar B, Leyhausen G, Günay H, Geurtsen W: Compatibility of resorbable and nonresorbable guided tissue regeneration membranes in cultures of primary human periodontal ligament fibroblasts and human osteoblast-like cells. *Clin Oral Investig* 2000; 4/4: 219-225.

Buchmann R, Hasilik A, Heinecke A, Lange DE: PMN responses following use of 2 biodegradable GTR membranes. *J Clin Periodontol* 2001; 28/11: 1050-1057.

Chang CY, Yamada S: Evaluation of the regenerative effect of a 25 % doxycycline-loaded biodegradable membrane for guided tissue regeneration. *J Periodontol* 2000; 71/7: 1086-1093.

Christgau M, Bader N, Schmalz G, Hiller KA, Wenzel A: Postoperative exposure of bioresorbable GTR membranes: effect on healing results. *Clin Oral Investig* 1997; 1/3: 109-118.

De Sanctis M, Zucchelli G, Clauser C: Bacterial colonization of barrier material and periodontal regeneration. *J Clin Periodontol* 1996; 23/11: 1039-1046.

Eickholz P, Kim TS, Holle R, Hausmann E: Long-term results of guided tissue regeneration therapy with non-resorbable and bioabsorbable barriers. I. Class II furcations. *J Periodontol* 2001; 72/1: 35-42.

Grimm WD, Cichon P, van der Hoeven H, Langendijk PS, Smith F, Worley MG, Schmitz I, Offenbacher S: The influence of sulfate-reducing bacteria colonization of 2 different bioresorbable barrier membranes for GTR. An 18-month case-controlled microbiologic and clinical study. *Int J Periodontics Restorative Dent* 2000; 20/1: 91-99.

Hung SL, Lin YW, Wang YH, Chen YT, Su CY, Ling LJ: Permeability of Streptococcus mutans and Actinobacillus actinomycetemcomitans through guided tissue regeneration membranes and their effects on attachment of periodontal ligament cells. *J Periodontol* 2002; 73/8: 843-851.

Hutmacher D, Hürzeler MB: Biologisch abbaubare Polymere und Membranen für die gesteuerte Gewebe- und Knochenregeneration. *Implantologie* 1995; 3/1: 21-37.

Hutmacher D, Hürzeler MB, Schliephake H: A review of material properties of biodegradable and bioresorbable polymers and devices for GTR and GBR applications. *Int J Oral Maxillofac Implants* 1996; 11: 667-678.

Kim TS, Holle R, Hausmann E, Eickholz P: Long-term results of guided tissue regeneration therapy with non-resorbable and bioabsorbable barriers. II. A case series of infrabony defects. *J Periodontol* 2002; 73/4: 450-459.

Kronenthal RL: Biodegradable polymers in medicine and surgery. *Polymer Sci Technol* 1975; 8: 119-137.

Minabe M, Kodama T, Kogou T, Fushimi H, Sugiyama T, Takeuchi K, Miterai E, Nishikubo S: Clinical significance of antibiotic therapy in guided tissue regeneration with a resorbable membrane. *Periodontal Clin Investig* 2001; 23/1: 20-30.

Nyman S, Lindhe J, Karring T, Rylander H: New attachment following surgical treatment of human periodontal disease. *J Clin Periodontol* 1982; 9/4: 290-296.

Ratka-Krüger P, Neukranz E, Raetzke P: Guided tissue regeneration procedure with bioresorbable membranes versus conventional flap surgery in the treatment of infrabony periodontal defects. *J Clin Periodontol* 2000; 27/2: 120-127.

Sculean A, Donos N, Miliauskaite A, Arweiler N, Brecx M: Treatment of intrabony defects with enamel matrix proteins or bioabsorbable membranes. A 4-year follow-up split-mouth study. *J Periodontol* 2001; 72/12: 1695-1701.

Simion M, Maglione M, Iamoni F, Scarano A, Piattelli A, Salvato A: Bacterial penetration through Resolut resorbable membrane in vitro. An histological and scanning electron microscopic study. *Clin Oral Implants Res* 1997; 8/1: 23-31.

Urbani G, Graziani A, Lombardo G, Caton JG: Clinical results with exposed polyglactin 910 resorbable membranes for guided tissue regeneration. *Int J Periodontics Restorative Dent* 1997; 17/1: 41-51.

Urbani G, Canepari P, Lombardo G, Salgarelli C, Santi E: [Effect of saliva on resorption time of some resorbable membranes]. *Minerva Stomatol* 1997; 46/11: 569-577.

Verderio E, Coombes A, Jones RA, Li X, Heath D, Downes S, Griffin M: Role of the cross-linking enzyme tissue transglutaminase in the biological recognition of synthetic biodegradable polymers. *J Biomed Mater Res* 2001; 54/2: 294-304.

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