Multivariate analysis of factors influencing outcomes of regenerative therapy: A retrospective study

Shyuan-Yow Chen, DDS,[a] Hom-Lay Wang, DDS, MSD,[b] Gerald N. Glickman, DDS, MS,[c] Yu Shyr, PhD,[d] and R. Lamont MacNeil, DDS, MdentSc[e]

[a]Department of Dentistry, Cathay General Hospital, Taipei, Taiwan, [b]Department of Periodontics/Prevention/Geriatrics, School of Dentistry, University of Michigan, Ann Arbor, MI, [c]Department of Endodontics, School of Dentistry, University of Washington, Seattle, WA, [d]Division of Biostatistics, Department of Preventive Medicine, School of Medicine, Vanderbilt University, Nashville, TN , and [e]Department of Periodontology, School of Dental Medicine, University of Connecticut Health Center, Farmington, CT, USA

Purpose: The purpose of this cross-sectional retrospective study was to determine the association between a defined set of clinical factors and treatment outcomes following regenerative therapy in a university-based specialty training program in Periodontics.

Materials and Methods: Data were collected from 131 sites in 82 patients who received various forms of regenerative therapy including barrier and/or bone grafting procedures. Clinical endpoints used in the analyses were reductions in probing pocket depth (PD) and radiographically detectable bone loss (RBL). Multivariate and univariate statistical analyses were used to determine the association between six patient-related factors and four outcome variables. The factors studied were: (1) age, (2) gender, (3) smoking, (4) use of bone allografts, barrier, or combined therapies, (5) position of margins of adjacent restorations, and (6) endodontic status of treated teeth. The four outcome variables were reduction in: (1) buccal PD, (2) lingual PD, (3) average PD, and (4) RBL.

Results: Results indicated an overall improvement in clinical health following therapy. A statistically significant reduction ($p<0.01$) was found for buccal PD (-1.53 ± 0.22 mm), lingual PD (-1.28 ± 0.22 mm) and average PD (-1.41 ± 0.20) while a 0.72 ± 0.23 mm reduction in RBL ($p<0.01$) was also noted. Multivariate analysis indicated that only two factors, increased age and smoking, had statistically significant negative effects on treatment outcomes. Univariate analysis indicated a statistically significant negative influence for 1) increasing patient age on buccal PD, lingual PD, and RBL reduction and 2) smoking on RBL reduction. Comparable clinical outcomes were found whether absorbable or non-absorbable barrier materials were used.

Conclusion: In summary, the findings suggest that increased age and smoking appear to be factors associated with poor or sub-optimal regenerative outcomes. **(Int Chin J Dent 2002; 2: 48-59.)**

INTRODUCTION

Although regenerative procedures, such as guided tissue regeneration (GTR) have become an accepted component of the periodontal surgical armamentarium, treatment outcomes remain largely unpredictable as evidenced by clinical studies which report varying success rates.[1-7] For example, Cortellini et al., using ePTFE (expanded-polytetrafluoroethylene) barrier material to treat 40 human intrabony defects, reported a gain of 2 mm or more probing attachment level in almost 90% of the treated sites.[3] Other researchers have observed less favorable results[6,7] including Selvig et al. who found comparable outcomes following GTR therapy surgery and conventional (non-GTR) flap debridement surgery.[7] These apparent inconsistencies in GTR treatment outcomes suggest that it is important to study factors (i.e. risk factors), which may adversely influence or limit treatment success.

Over the last decade, there has been an increasing interest in the identification of conditions or factors which may influence the initiation, progression, and/or treatment of periodontal diseases. Recent studies have reported age, gender, race, socio-economic status, smoking and general health states as risk indicators for periodontal disease.[8-11] Similar studies have also been conducted to define factors/conditions that may compromise or limit GTR therapy. Deep initial pockets, good oral hygiene, absence of gingival inflammation, absence of *Actinobacillus actinomycetemcomitans* infection, as well as the presence of connective tissue cells on the inner surface of the retrieved membrane have been shown to be associated with enhanced periodontal regeneration.[12] Machtei et al. suggested that good oral hygiene and frequent recall visits were essential for long-term stability of GTR outcomes.[13] Weigel et al. also concluded that a low incidence of gingival inflammation was a requirement for GTR success[14] while Tonetti et al. reported that control of oral hygiene and residual periodontal infection were important to achieve favorable results following both GTR and access flap surgical procedures.[15] In addition, factors such as tissue gain under the membrane, radiographic width of the defect angle, full mouth bleeding score, and presence or absence of flap coverage of the newly formed tissue have also been correlated with varying outcomes following regenerative therapy.[16] Hence, there is an emerging body of evidence that if certain operator and patient dependent variables are recognized and controlled, GTR therapy can become a more predictable treatment form.

Our knowledge to date regarding risk factors associated with sub-optimal GTR therapy outcomes has been derived largely from clinical studies conducted by highly trained clinicians in well-controlled research environments. Relatively little is known regarding factors which may be operative in a private practice setting or other less controlled treatment locations or situations. The purpose of this study was to identify factors associated with GTR treatment outcomes in a university-based advanced specialty training program in periodontics and to compare overall therapy outcomes with those of previously published reports. This information will be valuable since periodontal treatment in such programs, while supervised by trained periodontists, is performed by residents with varying and limited levels of clinical training, and these results may often differ from that of highly trained or experienced periodontists.

MATERIALS AND METHODS

Patient Population and Selection

This cross-sectional retrospective study utilized records of 713 previously treated patients from the University of Michigan, School of Dentistry, Graduate Periodontic Clinic patient pool. A record was considered eligible for analysis if the following criteria were fulfilled: (1) evidence of pre-surgical interproximal infrabony defects (≥3mm from the alveolar crest to the depth of defects) in periapical radiographs, (2) treatment of identified infrabony defects during the surgical corrective phase with a regenerative procedure involving either osseous grafting (i.e. decalcified freeze-dried bone allografts-DFDBA), GTR barrier/membrane or a combination of osseous grafting/GTR membranes, (3) availability of periapical radiographs taken at least 6 months after the regenerative surgery, and (4) absence of antibiotic use for 6 months prior to the surgical therapy. Based on these criteria, the eligible sample size was reduced to 82 patients including 36 males and 46 females ranging in age from 25 to 82 years old, with a mean age of 53 years. In total, 131 individual osseous defects were analyzed (i.e. 131 sites in 82 patients). The re-evaluation period after regenerative therapy ranged from 6 to 75 months, with a mean of 31 months.

Periodontal Treatment

Although treatment regimens varied due to multiple providers and different treatment protocols, each patient received standard initial therapy which included oral hygiene instruction and scaling and root planing. If periodontal surgery was indicated upon re-evaluation of initial therapy, it was performed following contemporary regenerative surgical principles. Surgical therapy was supervised by educationally-qualified faculty periodontists but performed by graduate students in either their first or second year of specialty training. In general, the surgical procedure involved the elevation of a full thickness mucoperiosteal flap with intracrevicular incisions, preserving as much keratinized marginal tissue as possible. Following thorough defect debridement and root planing, defects were treated by one of the three aforementioned regenerative techniques. Postsurgical protocols included daily rinsing with 0.12% chlorhexidine for the first 2 weeks and systemic doxycycline (100 mg/day) for 7 days. Sutures were removed 7 to 10 days after surgery and non-absorbable GTR barriers were retrieved 4 to 6 weeks after surgery. Following completion of the surgical therapy, patients were placed on a 3-month recall for supportive periodontal treatment.

Data Collection

All information was collected from patients' charts and radiographs. Outcome variable sets included (1) pre- and post-surgical probing depths (PD), measured in millimeters (mm) as measured with a Michigan “O” periodontal probe as the distance from the gingival margin to the base of the periodontal sulcus/pocket (both buccal and lingual sides were measured at interproximal contact areas) and (2) pre- and post-surgical radiographic bone loss (RBL), recorded in millimeters at interproximal areas on non-standardized periapical radiographs as the distance from the cemento-enamel junction to the most apical point of the alveolar bone within the infrabony defect. Treatment variables sets included: (1) age, i.e. $\leq$ or $\geq$ 45 years (2) gender, i.e. female or male, (3) history of smoking versus non-smoking (smoking = smokes more than one year of duration), (4) use of DFDBA, a GTR membrane (either non-absorbable or absorbable) or combination

(DFDBA + barrier) therapy; (5) presence or absence of endodontic treatment before surgery determined by presence or absence of permanent endodontic filling materials in periapical radiographs; and (6) presence or absence of a subgingival versus supragingival restoration margin adjacent to the osseous defect. Due to inconsistent data entry in the patients' records, it was not possible to analyze other important clinical information including plaque status, tooth mobility, amount of keratinized gingiva, and gingival recession.

Statistical Analysis

Data were analyzed using the SAS version 6.10 (SAS Institute, Cary, IN, USA) statistics program. All data were reported as means ± standard error (SE). A multivariate analysis (using restricted/residual maximum likelihood (REML)-based repeated measures model with compound symmetry covariance structure) was used to test the differences of assessment parameters (all risk factors were simultaneously analyzed in the model) over time. Tests concerning the differences of monitored parameters over time (e.g. PD and RBL) with different levels of a single risk factor (e.g. smoking vs. non-smoking) were completed using univariate analyses. All tests of significance were two-sided and statistically significant differences were recorded when $p \leq 0.05$.

RESULTS

Table 1 summarizes the demographic and treatment information for the study population. Records of 82 patients (56.1% females and 43.9% males) were reviewed. The 131 test sites analyzed displayed the following characteristics: 76 sites (58.0%) female versus 55 sites (42.0%) male; 39 sites (29.8%) in younger age group (< 45 years) versus 92 sites (70.2%) in older age group (≥ 45 years); 48 sites (36.6%) in non-smokers versus 83 sites (63.4%) in smokers; 63.4% of sites received DFDBA alone, 27% received DFDBA plus membrane while 9.9% received membrane placement alone.

Table 2 shows the mean changes in PD and RBL before and after regenerative treatment. The initial mean PDs were 6.27 ± 0.19 mm (buccal) versus 6.26 ± 0.18 mm (lingual) while the initial mean RBL was 5.07 ± 0.20 mm. Statistically significant reductions in PD and RBL were noted following regenerative treatment. Average PD reduction was 1.41 ± 0.20 mm ($p<0.01$) while a reduction of 0.72 ± 0.23 mm ($p<0.01$) was noted in RBL.

The relationship between four treatment outcome variables (i.e. buccal PD; lingual PD; average PD; and RBL) and six pre-clinical treatment factors (i.e. age, gender, smoking, use of bone grafts and/or membrane, endodontic status and status of adjacent restorative margins) were tested utilizing a multivariate analysis model. Only age and smoking were found to be correlated to buccal PD and RBL (Table 3). With respect to buccal PD, non-smokers had more buccal PD reduction (0.91 ± 0.52 mm, $p = 0.08$, marginal significance) and more RBL reduction (1.41 ± 0.44 mm, $p<0.01$) than smokers. Within the limited data set in this investigation, no other significant correlations were found among test factors in the multivariate analysis (Table 3).

Table 1. Demographic information.

Variable	Frequency (131 sites in 82 pts)	Percent (%)
Gender		
Female	76	58.0
Male	55	42.0
Age		
< 45	39	29.8
≥ 45	92	70.2
Smoking		
No	48	36.6
Yes		
1-9 cigarettes/day	9	6.9
10-19 cigarettes/day	10	7.6
> 19 cigarettes/day	19	14.5
unknown	45	34.4
Endodontic Treatment (Pre-regenerative Therapy)		
No	120	91.6
Yes	11	8.4
Restorative Status (Pre-regenerative Therapy)		
Without restoration	24	18.3
Supra-gingival margin	78	59.5
Sub-gingival margin	29	22.1
Type of Regenerative Therapy		
Barrier membrane alone	13	9.9
Bone graft alone	83	63.4
Combination of barrier and bone graft	35	26.7
Type of Barrier Membranes		
Absorbable	19	14.5
Non-absorbable	29	22.1

Table 2. Mean changes in monitored parameters.

	Before GTR therapy (mm ± S.E.) n = 131	After GTR therapy (mm ± S.E.) n = 131	Changes (mm ± S.E.)	P value
PD (Buccal)	6.27 ± 0.19	4.74 ± 0.17	-1.53 ± 0.22	0.0001
PD (Lingual)	6.26 ± 0.18	4.98 ± 0.16	-1.28 ± 0.22	0.0001
PD (Average)	-	-	-1.41 ± 0.20	0.0001
RBL†	5.07 ± 0.20	4.35 ± 0.21	-0.72 ± 0.23	0.0025

†Radiographic bone loss at proximal contact points.

Table 3. Effects of selected clinical factors on GTR outcome (Multivariate analysis).

	Changes (mm) ± S.E.: Pre- and Post-regenerative therapy			
	PD (Buccal)	PD (Lingual)	PD (Average)	RBL
Intercept	-3.11 ± 1.43 (p<0.05)	-0.40 ± 1.42 (p=0.78)	-1.87 ± 1.32 (p=0.16)	-1.17 ± 1.27 (p=0.36)
Sex				
F	0.26 ± 0.51 (p=0.61)	0.22 ± 0.49 (p=0.65)	0.27 ± 0.47 (p=0.58)	-0.68 ± 0.44 (p=0.12)
M	0.00	0.00	0.00	0.00
Age	0.05 ± 0.02 (p<0.01)*	0.001 ± 0.02 (p=0.97)	0.03 ± 0.02 (p=0.14)	0.04 ± 0.02 (p<0.05)*
Smoking				
No	-0.91 ± 0.52 (p=0.08)†	-0.53 ± 0.49 (p=0.28)	-0.73 ± 0.47 (p=0.13)	-1.41 ± 0.44 (p<0.01)*
Yes	0.00	0.00	0.00	0.00
Endodontic treatment				
No	-1.07 ± 0.75 (p=0.16)	-0.50 ± 0.78 (p=0.54)	-0.84 ± 0.70 (p=0.24)	-0.001 ± 0.69 (p=0.99)
Yes	0.00	0.00	0.00	0.00
Regenerative therapy				
Graft	-0.04 ± 0.65 (p=0.95)	0.13 ± 0.71 (p=0.86)	0.05 ± 0.60 (p=0.93)	-0.53 ± 0.63 (p=0.40)
Graft/Memb	0.53 ± 0.67 (p=0.43)	-0.35 ± 0.76 (p=0.65)	0.03 ± 0.63 (p=0.96)	0.35 ± 0.67 (p=0.60)
Memb	0.00	0.00	0.00	0.00
Status of restorative margin				
No	-0.12 ± 0.67 (p=0.86)	-0.67± 0.71 (p=0.35)	-0.32 ± 0.62 (p=0.61)	-0.78 ± 0.63 (p=0.22)
Supra	-0.16 ± 0.50 (p=0.75)	-0.51± 0.54 (p=0.35)	-0.21 ± 0.47 (p=0.66)	-0.42 ± 0.48 (p=0.39)
Sub	0.00	0.00	0.00	0.00

*Statistically significant at p<0.05 level. †Marginal significant level.

In univariate analysis, tests concerning the differences of PD and RBL over time among different levels of a single risk factor, such as age < 45 vs. age ≥ 45 and smoking vs. non-smoking, were completed (Table 4). The results are as follows:

Age < 45 vs. age ≥ 45

The younger age group (< 45) had more buccal PD reduction (1.55 ± 0.53 mm, p<0.01), more average PD reduction (1.08 ± 0.48 mm, p<0.05), and more RBL reduction (1.09 ± 0.48 mm , p < 0.05) than the older age (≥45) group. No significant findings were found for lingual PD.

Smoking vs. non-smoking

Non-smokers showed 1.25 ± 0.45 mm more RBL reduction than smokers (p<0.01). No significant findings were found when considering PD measurements.

Endodontically-treated teeth before regenerative therapy vs. non-endodontically treated teeth before regenerative therapy

There was a marginal significance for more buccal PD reduction (1.33 ± 0.74 mm, p = 0.08) in non-endodontically treated teeth when compared to endodontically treated teeth. No differences were noted in RBL.

Absorbable membrane vs. non-absorbable membrane

Buccal PDs were reduced 1.19 ± 0.54 mm (p<0.05) at sites treated with absorbable barriers when compared to sites treated with non-absorbable membranes sites. However, no significant findings were noted

when comparing lingual PD and only a marginal significance was found with the use of absorbable barriers when considering average PD reduction (p = 0.06) and RBL reduction (p = 0.06).

Table 4. Effects of selected clinical factors on GTR outcome (Univariate analysis).

	Changes (mm) ± S.E.: Pre- and Post-regenerative therapy			
	PD (Buccal)	PD (Lingual)	PD (Average)	RBL
Age				
Intercept	-1.17 ± 0.30 (p<0.01)	-1.15 ± 0.27 (p<0.01)	-1.17 ± 0.27 (p<0.01)	-0.36 ± 0.27 (p=0.19)
< 45	-1.55 ± 0.53 (p<0.01)*	-0.59 ± 0.49 (p=0.23)	-1.08 ± 0.48 (p<0.05)*	-1.09 ± 0.48 (p<0.05)*
≥ 45	0.00	0.00	0.00	0.00
Smoking (General)				
Intercept	-1.35 ± 0.34 (p<0.01)	-1.12 ± 0.30 (p<0.01)	-1.23 ± 0.30 (p<0.01)	-0.18 ± 0.29 (p=0.55)
No	-0.72 ± 0.52 (p=0.17)	-0.55 ± 0.47 (p=0.25)	-0.67 ± 0.46 (p=0.15)	-1.25 ± 0.45 (p<0.01)*
Yes	0.00	0.00	0.00	0.00
Smoking (Quantified)				
Intercept	-2.13 ± 0.70 (p<0.01)	-1.52 ± 0.60 (p<0.01)	-1.83 ± 0.60 (p<0.01)	-0.78 ± 0.54 (p=0.15)
0 cig/day	0.05 ± 0.80 (p=0.95)	-0.12 ± 0.70 (p=0.87)	-0.05 ± 0.69 (p=0.94)	-0.64 ± 0.62 (p=0.31)
1-9 cig/day	1.16 ± 1.27 (p=0.36)	0.38 ± 1.07 (p=0.72)	0.85 ± 1.09 (p=0.44)	0.67 ± 0.98 (p=0.49)
10-19 cig/d	-0.01 ± 1.44 (p=0.99)	0.30 ± 1.12 (p=0.79)	0.10 ± 1.22 (p=0.93)	-0.50 ± 1.10 (p=0.64)
> 19 cig/d	0.00	0.00	0.00	0.00
Endodontic treatment				
Intercept	-0.47 ± 0.71 (p=0.50)	-0.70 ± 0.70 (p=0.32)	-0.55 ± 0.64 (p=0.39)	-0.27 ± 0.67 (p=0.69)
No	-1.33 ± 0.74 (p=0.08)†	-0.71 ± 0.74 (p=0.34)	-1.08 ± 0.67 (p=0.12)	-0.48 ± 0.70 (p=0.50)
Yes	0.00	0.00	0.00	0.00
Type of membrane				
Intercept	-2.29 ± 0.43 (p<0.01)	-1.91 ± 0.43 (p<0.01)	-2.16 ± 0.38 (p<0.01)	-0.97 ± 0.36 (p<0.01)
Non-absorb	1.19 ± 0.54 (p<0.05)*	0.57 ± 0.55 (p=0.30)	0.91 ± 0.48 (p=0.06)†	0.87 ± 0.45 (p=0.06)†
Absorbable	0.00	0.00	0.00	0.00

*Statistically significant at p<0.05 level. †Marginal significant level.

DISCUSSION

Results from this study indicate that regenerative periodontal therapy conducted within the environment of an educational training program can achieve statistically significant reductions in PD (buccal -1.53 mm and lingual -1.28 mm) and RBL (0.72mm). This finding is in general agreement with a number of the previous studies,[4,7,17,18] which have reported 0.8 to 4.5 mm probing attachment level (PAL) gain, 1.2 to 4.3 mm bone gain, and 19% to 73% bone fill after 6 to 12 months when regenerative techniques were used in treatment of infrabony defects. More importantly, there is strong evidence that these clinical improvements can be maintained long-term following therapy. Machtei et al. reported that the rate of stability (change in PD ≤ 0.9 mm) was 90.9% and 90.4% for previously treated furcated and non-furcated sites respectively in their 4-year longitudinal study.[13] Weigel et al. also stated that 1.37 mm of new attachment could be maintained when compared to baseline data and 63.2% (12/19) of treated sites maintained clinical attachment level within ± 1 mm during the four years of maintenance following GTR therapy; no significant change in bone height was observed.[14] These findings are consistent with a 5-year longitudinal GTR study conducted by McClain and

Schallhorn (1993).[19]

In this study, the older age group (age ≥ 45 yrs.) had less favorable regenerative outcomes when compared to the younger age group (age under 45 yrs.). While it is not clear why aging may exert a negative effect upon regenerative therapy, it has been suggested that aging may change intrinsic host factors thus compromising the patient's ability to repair/regenerate tissues.[9,11,20-25] Van Der Velden reported that aging is accompanied by a greater susceptibility to periodontal disease and a slower rate of wound healing.[25] Several studies have reported that elderly patients tend to have slow wound healing when compared to younger individuals.[26-29] In contrast, Machtei et al. treated 30 patients aged from 27 to 66 years (mean 42.3 ± 9.8 years) with ePTFE membrane and concluded that age was not a significant factor in influencing the success of GTR treatment.[12] The differences in findings between these studies may be attributed to different populations studied and periodontal defects treated. In Machtei's study, 70 % of sites treated were in a younger age group (age under 45), whereas 70.2% of sites treated in this study were in the older age group (age ≥ 45). In addition, Machtei et al. analyzed only mandibular class II furcation involvement defects while all teeth types (single-rooted and multi-rooted teeth) were analyzed in the present study.

Non-smokers in this study had better regenerative outcomes than smokers, a finding in agreement with Tonetti et al. who reported that cigarette smoking is a factor strongly associated with reduced healing after GTR treatment.[30] According to Rivera-Hidalgo, smoking may inhibit host neutrophil function, reduce the circulation of gingival blood flow, and increase the mean proportion of anaerobes in the periodontal pocket.[31] Hanes et al. also showed that nicotine contained in cigarette binds to gingival fibroblasts and further affects normal fibroblast function.[32] However, the relationship between systemic effects of smoking and local etiologic factors in periodontal destruction and GTR outcome remains ill-defined. It has been proposed that smoking may exert a direct influence on the periodontium primarily by interfering with the body's response mechanisms rather than by augmenting local destructive factors such as plaque infection.[33] The level of cigarette consumption may also be an important factor in determining the overall effect of smoking on the healing response. Kaldahl et al. reported that heavy smokers (≥ 20 cigarettes/day) had less favorable outcomes than the light smokers (≤ 19 cigarettes/day) when conventional periodontal therapy is used while no difference was noted between past smokers and non-smokers.[34] In this study, information on the amount of daily cigarette use was not available and thus it was possible only to compare nonsmokers and smokers in terms of regenerative outcomes.

Using multivariate analysis, no significant correlations were found between clinical outcomes and gender, use of bone grafts, type of GTR barrier used, subgingival versus supragingival placement of restorative margins, and endodontic status. Univariate analysis demonstrated weak but positive correlations between i) non-endodontically treated teeth and ii) use of absorbable-type membranes with more favorable clinical outcomes. Non-endodontically treated teeth had more buccal PD reduction (1.33 ± 0.74 mm) when compared to endodontically treated teeth but this difference was only marginally significant ($p = 0.08$). In addition, it must be noted that the sample size of endodontically-treated teeth in this study was small ($n = 11$) representing only 8.4% of total study sites.

In terms of treatment variables, no significant differences were noted among the three treatment groups, e.g. DFDBA alone, GTR membrane alone, or GTR membrane combined with DFDBA. This finding is consistent with a number of earlier clinical studies.[5,7,35-37] Chen et al. failed to find any additional clinical benefit when DFDBA was used in conjunction with GTR barriers composed of bovine collagen.[37] Gouldin et al.,[38] in a six month study evaluating the use of GTR procedures in interproximal defects, found that either using ePTFE alone or in combination with DFDBA resulted in similar outcomes. In contrast, Reynolds and Bowers reported that concomitant use of DFDBA in GTR therapy results in significantly greater amounts of new periodontal attachment formation.[39] A number of protocol-related issues may partially explain these variations in findings, including differences in the measurement techniques used, the nature and extent of osseous defects treated, variations in oral hygiene and compliance levels between patients, and different commercial sources of DFDBA with varying levels of bioactive bone morphogenetic proteins within these preparations. The finding in this study that periodontal sites responded equally well whether absorbable or non-absorbable GTR barrier materials were used is also in general agreement with previous studies, including a recent report by Cortellini et al.[40]

There was no statistically significant influence on therapy outcomes when tissue responses adjacent to tooth surfaces without restorations were compared with subgingival restorations or with supragingival restorations. This finding may be due to the relatively small sample size for the first two groups (i.e. sites with no restorations, n = 24, or with subgingival margin placement, n = 29). Some differences between these groups were expected based on previous reports which suggested a detrimental influence of subgingival margins on periodontal health. Orkin et al. reported that tissues adjacent to crowns with subgingival margins had greater bleeding and recession compared with control sites.[41] Subgingival dental restorations are also thought to adversely affect the periodontium by promoting the retention of plaque, favoring development of a pathogenic flora, and/or by physically challenging the supracrestal attachment area.[42,43] However, in this study, these potentially negative influences were not detectable in therapy outcomes suggesting either a true lack of effect or to small sample size.

In comparison to controlled clinical studies, this study had a number of significant shortcomings and may be better defined as a multi-case analysis. In addition to other deficiencies, this retrospective study lacked a negative control group (e.g. flap surgery alone), drew data from a relatively small treatment pool, used non-standardized radiographs and non-calibrated measurement techniques, and used a variety of regenerative techniques performed by a member of beginning periodontal surgeons. Importantly, it should be recognized that cross-sectional studies can not show causality. However, the data is interesting in that even with these shortcomings in the treatment protocol, clinical outcomes approximated those published in numerous previous studies with respect to two specific clinical endpoints of therapy, i.e. reduction in i) depth (PD) and ii) radiographic bone loss (RBL). This finding suggests that regenerative therapy can be beneficial and relatively successful when performed in a clinical environment by practitioners who are not "experts" in such treatment modalities.

In summary, within the parameters of this study, the following conclusions were drawn: 1) Regenerative

therapy performed by multiple providers with varying levels of skill and experience resulted in an overall statistically significant reduction in probing depth (PD) and radiographic bone loss (RBL), 2) Aging and smoking appeared to exert negative influences on outcomes of regenerative therapy; 3) In univariate analyses, a weak negative correlation could be found between endodontically treated teeth and favorable GTR outcomes; 4) Adjunctive DFDBA grafting did not appear to significantly enhance regeneration; and 5) GTR procedures utilizing absorbable versus non-absorbable barriers showed comparable outcomes.

ACKNOWLEDGMENT

The authors wish to thank Drs. Maria Korsnes and Marianne Ong for their assistance in this study.

REFERENCES

1. Guillemin MR, Mellonig JT, Brunsvold MA. Healing in periodontal defects treated by decalcified freeze-dried bone allografts in combination with ePTFE membranes. (I). Clinical and scanning electron microscope analysis. J Clin Periodontol 1993; 20: 528-36.
2. Anderegg CR, Martin SJ, Gray JL, Mellonig JT, Gher ME. Clinical evaluation of the use of decalcified freeze-dried bone allograft with guided tissue regeneration in the treatment of molar furcation invasions. J Periodontol 1991; 62: 264-8.
3. Cortellini P, Pini-Prato G, Tonetti M. Periodontal regeneration of human infrabony defects. I. Clinical measures. J Periodontol 1993; 64: 254-60.
4. Cortellini P, Pini-Prato G, Tonetti M. Periodontal regeneration of human infrabony defects. II. Re-entry procedures and bone measures. J Periodontol 1993; 64: 261-68.
5. Caffesse RG, Nasjleti CE, Plotzke AE, Anderson GB, Morrison EC. Guided tissue regeneration and bone grafts in the treatment of furcation defects. J Periodontol 1993; 64: 1145-53.
6. Yukna RA. Clinical human comparison of expanded polytetrafluoroethylene barrier membrane and freeze-dried dura mater allografts for guided tissue regeneration of lost periodontal support. I. Mandibular molar class II furcation. J Periodontol 1992; 63: 431-42.
7. Selvig KA, Kersten BG, Wikesjö UME. Surgical treatment of intrabony periodontal defects using expanded polytetrafluoroethylene barrier membranes: Influence of defect configuration on healing response. J Periodontol 1993; 64: 730-3.
8. Johnson NW, Griffith GS, Wilton JMA, et al. Detection of high-risk groups and individuals for periodontal diseases. Evidence for the existence of high-risk groups and individuals and approaches to their detection. J Clin Periodontol 1988; 15: 276-82.
9. Griffiths GS, Wilton JMA, Curtis MA, et al. Detection of high-risk groups and individuals for periodontal diseases. Clinical assessment of the periodontium. J Clin Periodontol 1988; 15: 403-10.
10. Locker D, Leake JL. Risk indicators and risk markers for periodontal disease experience in older adults living independently in Ontario, Canada. J Dent Res 1993; 72: 9-17.
11. Arno A, Waerhaug J, Lovdal A, Schei O. Incidence of gingivitis as related to sex, occupation, tobacco consumption, toothbrushing, and age. Oral Surg Oral Med Oral Pathol 1958; 11: 587-95.
12. Machtei EE, Cho MI, Dunford R, Norderyd J, Zambon JJ, Genco RJ. Clinical, microbiological, and histological factors which influence the success of regenerative periodontal therapy. J Periodontol 1994; 65: 154-61.
13. Machtei EE, Grossi SG, Dunford R, Zambon JJ, and Genco RJ. Long-term stability of class II furcation defects treated with barrier membranes. J Periodontol 1996; 67: 523-7.
14. Weigel C, Brägger U, Hämmerle CHF, Mombelli A, Lang NP. Maintenance of new attachment 1 and 4 years following guided tissue regeneration (GTR). J Clin Periodontol 1995; 22: 661-9.
15. Tonetti MS, Pini Prato G, Cortellini P. Factors affecting the healing response of intrabony defects following guided tissue

regeneration and access flap surgery. J Clin Periodontol 1996; 23: 548-56.
16. Tonetti MS, Pini-Prato G, Cortellini P. Periodontal regeneration of human intrabony defects. IV. Determinants of healing response. J Periodontol 1993; 64: 934-40.
17. Becker W, Becker BE, Berg L, Prichard J, Caffesse R, Rosenberg E. New attachment after treatment with root isolation procedures: Report for treated class III and class II furcations and vertical osseous defects. Int J Periodontol Rest Dent 1988; 8: 8-23.
18. Handelsman M, Davarpanah M, Celletti R. Guided tissue regeneration with and without citric acid treatment in vertical osseous defects. Int J Periodontol Rest Dent 1991; 11: 350-63.
19. McClain PK, Schallhorn RG. Long-term assessment of combined osseous composite grafting, root conditioning, and guided tissue regeneration. Int J Periodontol Rest Dent 1993; 13: 9-27.
20. Grossi SG, Genco RJ, Machtei EE, et al. Assessment of risk for periodontal disease. II. Risk indicators for alveolar bone loss. J Periodontol 1995; 66: 23-9.
21. Grossi SG, Zambon JJ, Ho AW, et al. Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. J Periodontol 1994; 65: 260-7.
22. Haffajee AD, Socransky SS, Lindhe J, Kent RL, Okamoto H, Yoneyama T. Clinical risk indicators for periodontal attachment loss. J Clin Periodontol 1991; 18: 117-25.
23. Brown LJ, Oliver RC, Loe H. Evaluating periodontal status of US employed adults. J Am Dent Assoc 1990; 121: 226-32.
24. Hansen GC. An epidemiologic investigation of the effect of biologic aging on the breakdown of periodontal tissue. J Periodontol 1973; 44: 269-77.
25. Van Der Velden U. Effect of age on the periodontium. J Clin Periodontol 1984; 11: 281-94.
26. Abdellatif HM, Burt BA. An epidemiological investigation into the relative importance of age and oral hygiene status as determinants of periodontitis. J Dent Res 1987; 66: 13-8.
27. Papapanou PN, Wennström JL, Gröndahl K. Periodontal status in relation to age and tooth type. A cross-sectional radiographic study. J Clin Periodontol 1988; 15: 469-78.
28. Papapanou PN, Lindhe J, Sterrett JD, Eneroth L. Considerations on the contribution of aging to loss of periodontal tissue support. J Clin Periodontol 1991; 18: 611-5.
29. Cortellini P, Pini-Prato G, Tonetti M. Periodontal regeneration of human infrabony defects (V). Effect of oral hygiene on long-term stability. J Clin Periodontol 1994; 21: 606-10.
30. Tonetti MS, Pini-Prato G, Cortellini P. Effect of cigarette smoking on periodontal healing following GTR in infrabony defects. A preliminary retrospective study. J Clin Periodontol 1995; 22: 229-34.
31. Rivera-Hidalgo F. Smoking and periodontal disease. A review of the literature. J Periodontol 1986; 57: 617-24.
32. Hanes PJ, Schuster GS, Lubas S. Binding, uptake, and release of nicotine by human gingival fibroblasts. J Periodontol 1991; 62: 147-52.
33. Bergström J, Eliasson S, Preber H. Cigarette smoking and periodontal bone loss. J Periodontol 1991; 62: 242-6.
34. Kaldahl WB, Johnson GK, Patil KD, Kalkwarf KL. Levels of cigarette consumption and response to periodontal therapy. J Periodontol 1996; 67: 675-81.
35. Wallace SC, Gellin RG, Miller MC, Mishkin DJ. Guided tissue regeneration with and without decalcified freeze-dried bone in mandibular class II furcation invasions. J Periodontol 1994; 65: 244-54.
36. Becker W, Lynch SE, Lekholm U, et al. A comparison of ePTFE membranes alone or in combination with platelet-derived growth factors and insulin-like growth factor-I or demineralized freeze-dried bone in promoting bone formation around immediate extraction socket implants. J Periodontol 1992; 63: 929-40.
37. Chen CC, Wang HL, Smith F, Glickman GN, Shyr Y, O'Neal RB. Evaluation of a collagen membrane with and without bone grafts in treating periodontal intrabony defects. J Periodontol 1995; 66: 838-47.
38. Gouldin AG, Fayad S, Mellonig JT. Evaluation of guided tissue regeneration in interproximal defects. (II) Membrane and bone versus membrane alone. J Clin Periodontol 1996; 23: 485-91.
39. Reynolds MA, Bowers GM. Fate of demineralized freeze-dried bone allografts in human intrabony defects. J Periodontol 1996; 67: 150-7.

40. Cortellini P, Pini-Prato G, Tonetti M. Periodontal regeneration of human intrabony defects with bioresorbable membranes. A controlled clinical trial. J Periodontol 1996; 67: 217-23.
41. Orkin DA, Reddy J, Bradshaw D. The relationship of the position of crown margins to gingival health. J Prosthet Dent 1987; 57: 421-4.
42. Brunsvold MA, Lane JJ. The prevalence of overhanging dental restorations and their relationship to periodontal disease. J Clin Periodontol 1990; 17: 67-72.
43. Jansson L, Ehnevid H, Lindskog S, Blomlöf L. Proximal restorations and periodontal status. J Clin Periodontol 1994; 21: 577-82.

Reprint request to:

Dr. Hom-Lay Wang
University of Michigan, School of Dentistry
1011 N. University Ave., Ann Arbor, Michigan 48109-1078, USA
FAX: +1-734-936-0374
E-mail: homlay@umich.edu

Received on September 22, 2001. Revised on December 24, 2001. Accepted on December 26, 2001.