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Host response to microbial challenge following resective/ non-resective periodontal therapy

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Abstract

Background: The host response to microbial challenge depends on the recruitment of homing leucocytes and may be related to the experience to infectious insults over years.

Purpose: The aim of this study was to investigate the soft tissue reactions to de novo plaque formation at sites treated with either open flap debridement or with the use of resective means during periodontal therapy.

Material and Methods: Fifteen patients, who had been treated for periodontal disease (severe generalized chronic periodontitis), participated in the study. Surgical therapy was performed using either gingivectomy (GV) or open flap debridement (OFD) procedures in a split mouth design. After 6 months of healing (day 0), two gingival biopsies were obtained, one from the GV- and one from the OFD-treated sites. The experimental gingivitis model was applied and plaque accumulation was allowed for 3 weeks. New biopsies were obtained from the remaining quadrants on day 21 of plaque formation. The biopsies were snap frozen and prepared for immunohistochemical analysis.

Results: Following 3 weeks of plaque accumulation, the size of the lesion in OFD sites was more than twice as large than that in GV sites (0.42 *versus* 0.19 mm^2). In the GV units, the lesion was characterized by almost similar proportions of T cells ($CD3^+$, 6.0%) and B cells ($CD19^+$, 6.6%), while the ICT in OFD sites was dominated by B cells (13.8%). During the 3-week period of plaque formation the increase in cell densities of T and B cells was three times larger in OFD than in GV sites. The proportion of ELAM-1 ($CD62^+$ cells) decreased in GV (-0.4%) and increased in OFD (0.9%) sites.

Conclusions: The host response that occurred in the gingival sites treated with OFD was more pronounced than the reaction that under similar experimental conditions took place in the regenerated gingiva at sites treated by resective means.

Key words: B-lymphocytes; cell adhesion molecules; experimental gingivitis; immunohistochemistry; immunology; periodontal therapy; periodontitis

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The experimental gingivitis model (Löe et al. 1965) has been used to study the soft tissue reaction to the formation of biofilms at teeth (Payne et al. 1975, Seymour et al. 1983, van der Velden et al. 1985, Abbas et al. 1986, Brecx et al. 1987, Fransson et al. 1996, 1999) and implants (Pontoriero et al. 1994, Zitzmann et al. 2001, 2002). Zitzmann et al. (2001) collected soft tissue biopsies from tooth and implant sites in the same subjects and reported that after 3 weeks of undisturbed plaque formation, the inflammatory lesion in the ginigiva at the teeth had become almost twice as large as in the peri-implant mucosa. It was suggested that (i) the host response to plaque formation was more pronounced in the gingiva than in the peri-implant mucosa and that (ii) this difference – at least in part – might be explained by the length of time during which the two different soft tissue units had been exposed to the oral environment. Thus, while the peri-implant mucosa in the subject sample was ''a relative newcomer'', the tooth/gingiva

interface had been exposed to plaque antigens for many years and developed an ample and effective local immune defense (Liljenberg et al. 1997, Zitzmann et al. 2001).

Fransson et al. (1996, 1999) compared the host response to plaque in gingival specimens obtained from young and old individuals. It was reported that the inflammatory lesions (ICT) were larger and had higher B-cell densities in older subjects than those in the younger subjects. It was suggested that the differences between young and old subjects were related to their different experience to microbial challenge (Fransson et al. 1999).

The aim of the present study was to test the hypothesis that the ''experience'' of the local immune defense, i.e. the inflammatory cell infiltrate in the gingiva, may influence the soft tissue reaction to de novo plaque formation.

Material and Methods

The local human ethics committee at the University of Basel approved the study protocol. Fifteen patients with severe chronic periodontitis participated in the study. Prior to enrollment, the subjects gave their informed consent. Details regarding patient selection and examination procedures were described by Zitzmann et al. (2005). In each patient, two different surgical methods were employed in the treatment of periodontitis sites. Thus, in two randomly selected quadrants (one in the maxilla and one in the mandible), pockets were eliminated by soft tissue resection (gingivectomy (GV)), while in the contralateral quadrants, a non-resective approach with open flap debridement (OFD) was utilized (Zitzmann et al. 2005).

Following a 6-month period of plaque control, a clinical examination was performed that included the assessment of probing pocket depth (PPD), probing attachment level (PAL), soft tissue recession from the CEJ (Rec), bleeding on gentle probing (BoP^+), amount of plaque (PlI, Silness & Löe 1964) and gingivitis (MGI, Lobene et al. 1986) at four surfaces of all teeth. Two gingival biopsies were harvested, one from a GV-treated site and one from an OFD-treated site (day 0, Table 1). The biopsies were snap frozen and prepared for immunohistochemical analysis. Details regarding biopsy sampling, immunohistochemical preparation and methods applied for the histological analyses were previously reported (Zitzmann et al. 2005). The CD3 monoclonal antibody was used to identify T cells, the CD4 marker detected T-helper cells and the CD8 marker cytotoxic T cells. B cells were identified by CD19 monoclonal antibodies and polymorphonuclear leucocytes with anti-PMN elastase monoclonal antibodies. CD54, CD62E, CD106 and BMS170 cell markers were used to identify endothelial cells that expressed the intercellular (ICAM), endothelial (ELAM), vascular (VCAM) and mucosal vascular addressin (MAdCAM-1) cell adhesion molecules.

The participants were asked to abstain from all mechanical and chemical plaque control measures for a period of 3 weeks. On day 21, PlI and MGI were scored and biopsies sampled from two additional sites, one GV- and one OFD-treated site (Table 1).

Statistical analysis

Mean values ± standard deviations (SD) were calculated for each variable and using the subject as the experimental unit. Differences between the two treatment procedures (GV *versus* OFD) on day 0 (6 months following surgical therapy) and on day 21 (3 weeks of plaque formation) were analyzed using the Student's *t*-test for paired observations. p-values < 0.05, adjusted for multiple testing (Miller 1981), were considered significant.

Results

Clinical observations

On day 0, the mean PPD was significantly smaller (1.9 ± 0.5 *versus* 2.9 ± 0.7 mm) and the amount of recession significantly larger (4.2 ± 1.5 *versus* 3.2 ± 1.3 mm) in GV than in OFD sites. The PAL was similar at GV and OFD units (6.0 ± 1.5 and 6.1 ± 1.1 mm). In both groups, the PII (GV 0.09 ± 0.20, OFD 0.13 ± 0.22) and the MGI scores (GV 0.13 ± 0.22, OFD 0.25 ± 0.26) were low. Only three sites, one in GV- and two in OFD-treated sites exhibited BoP.

On day 21, all tooth surfaces harboured plaque and exhibited clinical signs of inflammation (Fig. 1a, b). The mean MGI scores were 2.40 ± 0.51 (GV) and 2.47 ± 0.52 (OFD).

Histological findings

Day 0

All biopsies sampled on day 0 were found to harbour a small inflammatory

Table 1. Tooth sites examined and subsequently exposed to biopsy at day 0, i.e. 6 months following resective gingivectomy (GV) and non-resective open flap debridement (OFD) therapy, and at day 21, i.e. 3 weeks of no mechanical plaque control

Patient	Age (years)	Day 0 (6 months healing)		Day 21 (experimental gingivitis)	
		GV	OFD	GV	OFD
1. C. B.	50	14	23	34	44
2. L. A.	56	44	34	24	15
3. S. Z.	55	45	34	13	23
4. W. A.	57	23	13	43	35
5. W. Y.	56	24	15	35	45
6. P. W.	57	14	23	34	43
7. M. C.	67	24	15	34	44
8. H. W.	66	13	24	44	33
9. P. F.	56	43	33	25	15
10. K. C.	69	22	13	35	43
11. M. E.	43	44	34	23	15
12. T.H.	52	45	34	22	12
13. J. S.	56	45	35	24	14
14. M. B.	38	34	44	25	15
15. P. D.	63	44	33	13	24
Mean	56.07				
SD	8.40				

Location of the tooth site in the 1st–4th quadrant is described using the FDI system.
All biopsies were harvested from interproximal sites.

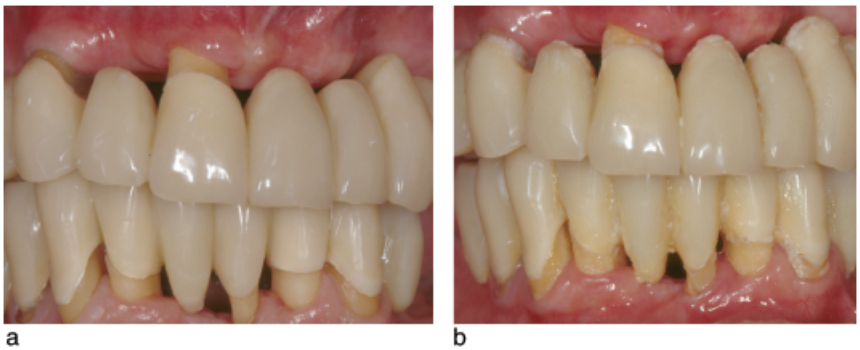

Fig. 1. Clinical photograph of subject no. 4. (a) At day 0 following 6 months of healing and (b) after 3 weeks of plaque accumulation (day 21).

Table 2. Biopsies obtained at day 0; results of the morphometric measurements

Treatment	GV	*p*-value ($n = 15$)	OFD
Size ICT (mm^2)	0.08 (0.04)	0.002*	0.19 (0.10)
% of ICT			
CD3	4.52 (2.00)	0.152	5.39 (2.14)
CD4	3.21 (1.93)	0.320	3.73 (1.78)
CD8	1.42 (0.59)	0.042	1.82 (0.85)
CD19	5.41 (2.48)	0.0001*	10.06 (3.21)
Elastase	0.51 (0.36)	0.008*	0.88 (0.35)
CD54	3.99 (1.21)	0.149	4.73 (1.87)
CD62	1.76 (0.92)	0.561	1.91 (0.79)
CD106	4.81 (0.71)	0.128	5.31 (1.40)
BMS 170	0.13 (0.13)	0.040	0.30 (0.30)
CD3/CD19 ratio	0.99 (0.51)	0.021	0.60 (0.34)

Mean values and standard deviations (SD).
*Statistically significant difference between gingivectomy (GV) and open flap debridement (OFD) treatment.

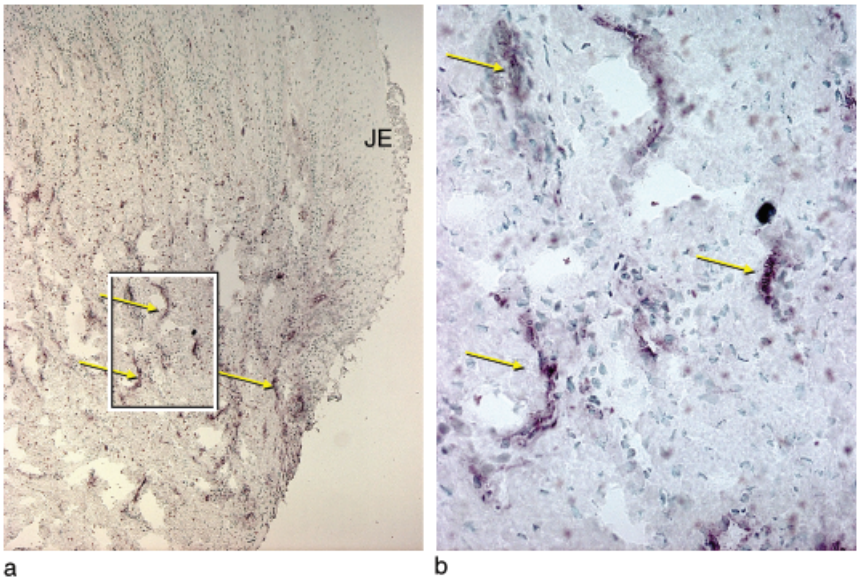

Fig. 2. Bucco-lingual section of a biopsy from a site treated with gingivectomy and sampled on day 0 (subject no. 4). Vascular cell adhesion molecules (VCAM) labeling (a) original magnification × 100, JE, junctional epithelium. Arrows indicate vascular structures expressing VCAM. (b) Higher magnification (× 400) of the area outlined in (a). $CD106^+$ cells are indicated by arrows.

cell infiltrate (ICT) that consistently was located in the connective tissue immediately lateral to a junctional epithelium, the marginal portion of which included few neutrophilic leucocytes and isolated lymphocytes. The size and cellular composition of the ICT varied between biopsies sampled from GV- and OFD-treated sites. Thus, the lesion at OFD sites occupied a larger area (0.19 ± 0.1 *versus* $0.08 \pm 0.04\,mm^2$, Table 2) and contained significantly larger proportions of $CD19^+$ cells ($10.1 \pm 3.2\%$ *versus* $5.4 \pm 2.5\%$) and $elastase^+$ cells ($0.9 \pm 0.4\%$ *versus* $0.5 \pm 0.4\%$) than GV sites. The densities of endothelial cell markers ($CD54^+$, $CD62^+$, $CD106^+$ cells) varied between 1.8% and 5.3% (Figs 2 and 3). The endothelial cell marker MAd-CAM-1 ($BMS170^+$ cells) was detected in 12 of the 15 subjects, and occurred in eight GV and 11 OFD sites.

Day 21

The inflammatory lesions that occurred in specimens representing day 21 were more than twice as large in the OFD (0.42 ± 0.19 *versus* $0.19 \pm 0.14\,mm^2$) than in the GV biopsies (Table 3). The lesions at OFD sites contained larger proportions of $CD3^+$ ($9.7 \pm 4.3\%$ *versus* $6.0 \pm 1.9\%$) and $CD19^+$ cells ($13.8 \pm 4.7\%$ *versus* $6.6 \pm 2.7\%$) than the corresponding ICT of GV sites (Figs 4 and 5). Further, the proportions of $CD8^+$ ($2.3 \pm 0.9\%$ *versus* $1.3 \pm 0.6\%$) and $elastase^+$ cells ($1.3 \pm 0.6\%$ *versus* $0.6 \pm 0.4\%$) were also greater in OFD than in GV sites.

The proportions of endothelial cell markers ($CD54^+$, $CD62^+$, $CD106^+$ cells) varied between 1.4% and 5.0% and were significantly larger in the OFD sites than in the GV sites.

In eight subjects, MAdCAM-1 ($BMS170^+$ cells) expression was found in both GV and OFD sites. In four subjects, the MAdCAM-1 expression was confined to the OFD-treated sites, while no $BMS170^+$ cells were detected in the remaining three subjects.

Changes between days 0 and 21

In both OFD- and GV-treated sites, the size of the inflammatory lesion increased during the 3 weeks of no plaque control. The enlargement of the ICT was more marked in OFD than in GV (0.23 ± 0.18 *versus* $0.11 \pm 0.13\,mm^2$, Table 4).

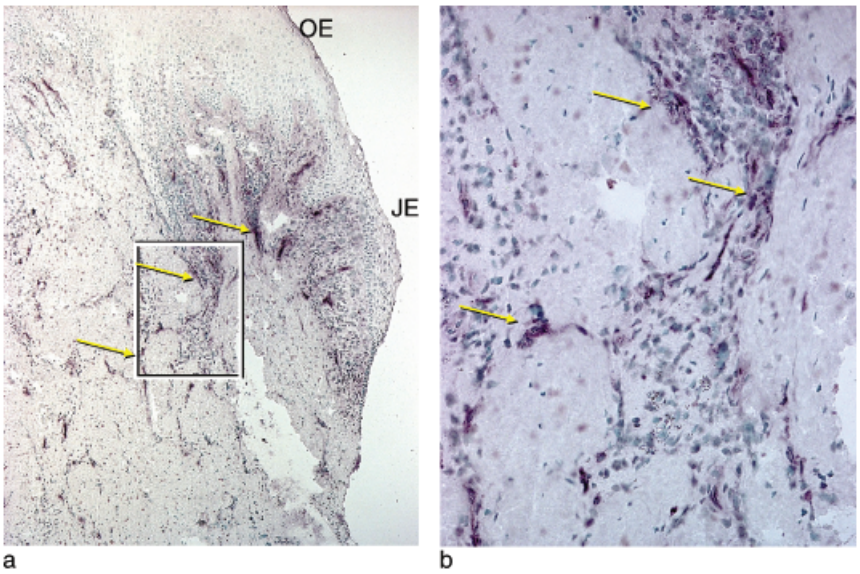

Fig. 3. Bucco-lingual section of a biopsy from a site treated with open flap debridement and sampled on day 0 (subject no. 4). Vascular cell adhesion (VCAM) labeling (a) original magnification × 100, OE: oral epithelium, JE, junctional epithelium. Arrows indicate vascular structures expressing VCAM. (b) Higher magnification (× 400) of the area outlined in (a). $CD106^+$ cells are indicated by arrows.

Table 3. Biopsies obtained after 3 weeks of experimental gingivitis (day 21); results of the morphometric measurements

Treatment	GV	*p*-value ($n = 15$)	OFD
Size ICT (mm^2)	0.19 (0.14)	0.001*	0.42 (0.19)
% of ICT			
CD3	6.02 (1.87)	0.007*	9.70 (4.27)
CD4	4.79 (1.88)	0.028	7.45 (3.69)
CD8	1.28 (0.64)	0.001*	2.30 (0.91)
CD19	6.61 (2.65)	<0.0001*	13.84 (4.69)
Elastase	0.55 (0.36)	0.0007*	1.25 (0.59)
CD54	2.84 (0.86)	0.005*	3.74 (0.97)
CD62	1.37 (0.78)	0.0007*	2.81 (1.37)
CD106	3.54 (1.05)	<0.0001*	4.96 (0.88)
BMS 170	0.30 (0.38)	0.034	0.69 (0.62)
CD3/CD19 ratio	1.09 (0.59)	0.099	0.76 (0.37)

Mean values and standard deviations (SD).
*Statistically significant difference between gingivectomy (GV) and open flap debridement (OFD) treatment.

In GV sites as well as in OFD sites, the increase in ICT was accompanied by an increase in the proportion of $CD3^+$ and $CD19^+$ cells. In the OFD-treated sites, the change in the densities of T and B cells was approximately three times higher than in the corresponding GV-treated sites (4.3% *versus* 1.5% and 3.8% *versus* 1.2%).

During the experimental period, the densities of the endothelial cell markers CD54, CD62 and CD106 decreased. $CD62^+$-cell proportions also decreased in GV ($-0.4 \pm 1.4\%$) but increased in OFD units ($0.9 \pm 1.3\%$, Table 4).

Discussion

The present investigation demonstrated that a residual inflammatory cell infiltrate, in comparison with a newly formed gingival lesion, responded to 3 weeks of de novo plaque exposure by becoming larger and including higher proportions of B cells, T cells and neutrophils. In other words, the host response that occurred in the gingival sites treated with OFD was more pronounced than the reaction that under similar experimental conditions took place in the newly regenerated gingiva at sites treated by resective means (GV).

In the current study, the experimental gingivitis model was applied in subjects who had been exposed to two different surgical methods of periodontal treatment. A comparison of the host response between different tooth regions within the same subjects was hereby made possible. In previous studies the experimental gingivitis model was used to investigate the inflammatory reaction between different groups. Abbas et al. (1986) selected two groups of patients of different age and who had been treated for advanced periodontal disease. The younger age group (25–39 years) was intended to represent individuals with a higher degree of susceptibility to periodontal disease than the group of older subjects (45–54 years). Two years following completion of the surgical treatment experimental gingivitis was performed. The histological analysis of gingival biopsies did not reveal any differences between the two groups (Abbas et al. 1986). Fransson et al. (1996, 1999) used the experimental model to evaluate the host response to plaque in periodontally healthy young (20–25 years) and old subjects (65–80 years). Gingival biopsies were obtained at days 0, 7 and 21 of plaque formation. It was reported that during the 3-week period of plaque accumulation, older subjects developed a larger sized ICT with a greater proportion of B cells than younger subjects. The authors suggested that the differences in host response in the two groups were related to local defense mechanisms in the gingiva. In some respects the differences between young and old subjects reported by Fransson et al. (1999) are in accordance with data from the current experiment on GV- and OFD-treated sites. Thus, plaque formation at sites treated with non-resective methods (OFD; ''old gingiva'') resulted in larger ICT and higher B-cell proportions than at sites exposed to resective procedures (GV; ''young gingiva'').

In a previous study from our group, the experimental gingivitis model was applied to healthy tooth and implant sites in the same individuals (Zitzmann et al. 2001). Soft tissue biopsies were obtained before and after de novo plaque accumulation. It was reported that on day 0 small inflammatory cell lesions, which contained similar proportions of T and B cells were found both in tooth and implant sites. At day 21 of

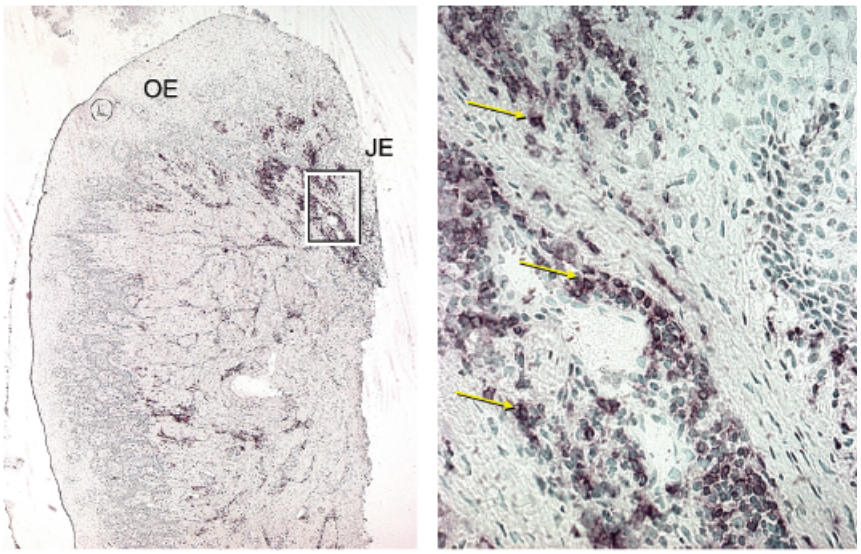

Fig. 4. Bucco-lingual section of a biopsy from a site treated with gingivectomy and sampled on day 21 (subject no. 4). CD19 labeling (a) original magnification × 50, OE, oral epithelium; JE, junctional epithelium. (b) Higher magnification (× 400) of the area outlined in (a). $CD19^+$ cells are indicated by arrows.

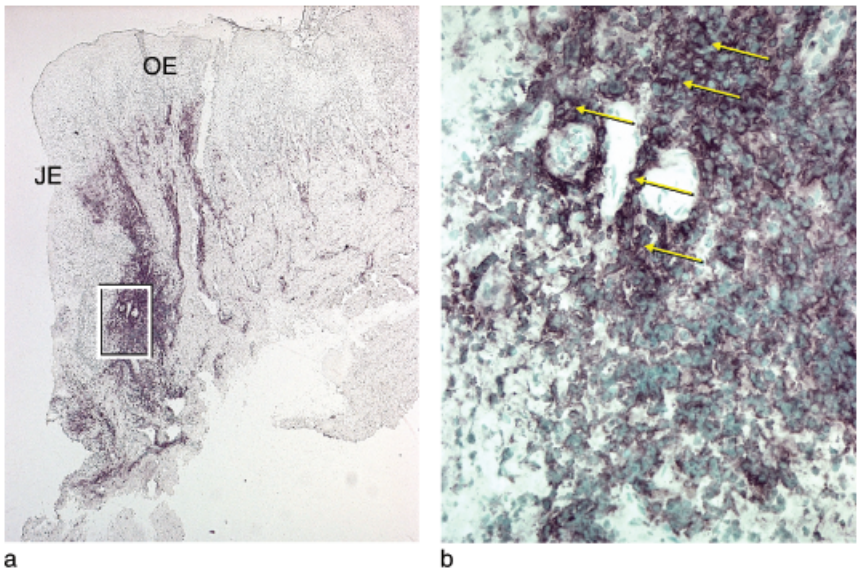

Fig. 5. Bucco-lingual section of a biopsy from a site treated with open flap debridement and sampled on day 21 (subject no. 4). CD19 labeling (a) original magnification × 50, OE, oral epithelium; JE, junctional epithelium. (b) Higher magnification (× 400) of the area outlined in (a). $CD19^+$ cells are indicated by arrows.

plaque exposure, the proportions of all inflammatory cell markers had increased in both tissue types. The increase in the size of the lesion and the rise in cell densities tended to be more pronounced in the soft tissues at the tooth than in the implant sites. The findings in the study by Zitzmann et al. (2001) are in agreement with data reported in the present study. The changes in T- and B-cell densities that occurred during the experimental period were thus about three times greater in OFD than in GV sites.

In the present investigation, small changes of the proportions of activated cell adhesion molecules within the ICT were observed during the experimental period. Differences between GV and OFD were only detected for the endothelial cell adhesion molecules (ELAM-1), which increased in OFD but decreased in GV sites. A similar response to plaque accumulation was reported in the comparative study on implants and teeth by Zitzmann et al. (2001) previously referred to. Thus, during the 21 days of plaque formation, the proportion of $CD62^+$-endothelial cells increased in the tooth sites but decreased in the implant units. It was suggested that during the course of the development of inflammation at implants, a cytokine-mediated downregulation of the endothelial cell activation occurred. The observations made at implants in the study by Zitzmann et al. (2001) are comparable with the reactions at the GV sites in the present study.

Hannigan et al. (2004) examined different soluble cell adhesion molecules (sICAM, sVCAM and sE-selectin) in gingival crevicular fluid sampled from healthy, gingivitis and periodontitis sites. Larger amounts of sVCAM were found in gingivitis than in healthy samples obtained from different subjects. Small variations in the amount of CAMs were, however, observed between healthy and diseased sites in the same individual (Hannigan et al. 2004). Del Castillo et al. (1996) analyzed the expression of the vascular cell adhesion molecule (VCAM-1) and VLA integrins (very late activation glycoproteins). Gingival biopsies were obtained from clinically healthy and gingivitis units and from sites exhibiting moderate to advanced periodontitis. It was observed that the expression of VCAM-1 was detectable in the majority of the small blood vessels in all types of samples. VLA-positive cells, however, increased gradually with the severity of the disease as well as with the density of the infiltrate and with the number of $CD19^+$ cells. Del Castillo et al. (1996) suggested that the increase of inflammatory cells beneath the pocket epithelium in periodontitis samples reflects the enhanced expression of cell adhesion molecules as the resulting response to the chronic stimulus of microbial agents. The findings regarding the variation in VCAM expression with inflammation reported by Hannigan et al. (2004) and Del Castillo et al. (1996) are also in agreement with observations made in the current investigation.

Table 4. Results of the calculated changes between day 0 (6 months of healing) and day 21 (experimental gingivitis) in sites treated with gingivectomy (GV) and open flap debridement (OFD)

Treatment	GV	*p*-value ($n = 15$)	OFD
Size ICT (mm^2)	0.11 (0.13)	0.042	0.23 (0.18)
% of ICT			
CD3	1.50 (2.83)	0.021	4.32 (3.33)
CD4	1.59 (2.85)	0.064	3.73 (3.14)
CD8	− 0.14 (0.82)	0.050	0.48 (1.10)
CD19	1.20 (2.90)	0.037	3.78 (3.51)
Elastase	0.04 (0.49)	0.106	0.37 (0.72)
CD54	− 1.15 (1.28)	0.791	− 0.99 (2.05)
CD62	− 0.39 (1.39)	0.005*	0.89 (1.32)
CD106	− 1.28 (1.41)	0.100	− 0.36 (1.83)
BMS 170	0.17 (0.34)	0.166	0.39 (0.55)
CD3/CD19 ratio	0.10 (0.68)	0.778	0.15 (0.20)

Mean values and standard deviations (SD).
Decreased values are presented with (−).
*Statistically significant difference between GV and OFD treatment.

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