The susceptible individual in periodontal and implant treatment

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Avancerade former av marginal parodontit drabbar endast en liten del av den vuxna befolkningen. Det har anförts att dessa individer har försämrad motståndskraft mot det bakteriella angreppet. I denna översikt belyses de lokala och systemiska immunologiska egenskaperna hos en grupp individer med avancerad parodontal sjukdom, liksom förändringarna hos immunologiska parametrar efter lyckad parodontal behandling. Benägenheten att utveckla plackassocierade lesioner i vävnaderna runt implantat diskuteras och några histopatologiska karakteristika hos peri-implantit-lesioner beskrivs.

Although it is generally accepted that advanced periodontal disease only affects a small portion of an adult population [1], the unique features of periodontitis-susceptible subjects have not been completely elucidated. Attempts have been made to describe the subgingival microflora, including specific putative periodontal pathogens, as a dominate aetiologic factor [2] while, on the other hand, disturbances within the host response have been suggested to play a decisive role for the initiation and perpetuation of periodontal disease [3]. Recent data have further supported the concept that host factors, including genetic components, have a strong association with periodontal disease [4]. Kornman et al. [4] reported that severity of periodontal disease, at least in non-smoking subjects, was associated with a genotype for two interleukin-1 polymorphisms and that such genetic markers could be used to identify periodontitis-susceptible subjects.

This review focuses on host response characteristics of individuals susceptible to periodontal disease. In particular, systemic and local immunological factors will be emphasised and the effect of periodontal therapy on such parameters described. In addition, tooth loss in periodontitis-susceptible individuals may call for implant therapy. It is not clear whether susceptibility to periodontal disease will interact with the long-term prognosis for dental implants. The mechanism by which the immune competence in the peri-implant mucosa is established and the tissue reaction to plaque will be discussed. In addition, some histopathological features of peri-implantitis lesions will be illustrated.

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The periodontitis lesion

Tissue destruction is one of the hallmarks of periodontal disease. The detailed mechanism by which the host tissue is destroyed and which factors control the host response to the subgingival microbiota are at present not entirely understood. It is generally accepted, however, that bacteria (including their products) *per se* may not cause significant tissue destruction, while the resulting host response and subsequent inflammatory process may lead to substantial connective tissue degradation and bone resorption [5]. The morphological features of a periodontitis site are well described [6]. Thus, a subgingival microbiota occupies the pocket compartment and an inflammatory infiltrate (ICT) is established in the gingival connective tissue lateral to a pocket epithelium (Fig. 1). The cells within the ICT have been described with respect to their morphological characteristics [7] and phenotypic and/or functional features [8–15]. Thus, lymphocytes and plasma cells seem to be the dominating cell types in lesions of adult periodontal disease and the T-helper (CD4 positive) lymphocytes occur in higher numbers than do cytotoxic (CD8 positive) T cells. In addition, the majority of

Figure 1. Mesiodistal section of a human periodontitis site with evident loss of attachment and alveolar bone. Note the subgingival plaque and calculus on the root surface and the pocket epithelium lining the inflammatory infiltrate in the gingival tissue.

lymphocytes in periodontitis lesions are of the memory phenotype (CD45RO) [16, 17]. While the CD4/CD8 ratio in clinically healthy gingival tissue and gingivitis lesions is considered to be similar to that found in peripheral blood, a decline is observed for the corresponding ratio in periodontitis sites [9, 14, 18]. In a study on progression of periodontal disease, Liljenberg et al. [19] observed that the number of CD4-positive cells was increased in sites which during the period of monitoring exhibited further attachment loss, and that the CD4/CD8 ratio in such lesions was higher than in non-progressing lesions in the same patient.

T-cell receptor V α/β phenotypes

The lymphocytes of the periodontitis lesion are involved in specific immune reactions in which the T-cell receptor (TCR) will interact with the processed antigen in association with class II molecules. While the majority part (>95%) of the T cells in peripheral blood display the TCR V α and β chain, the remaining fraction contain the γ/δ type. The α/β TCR, in contrast to the γ/δ type, will recognise processed antigens in conjunction with the class II molecule [20]. In several autoimmune diseases, different expressions of the TCR V α/β phenotype have been observed. In particular, multiple sclerosis and rheumatoid arthritis are associated with different α/β TCR genes [21, 23]. Oral diseases have, in addition, been associated with various TCR genes. Thus, Simark-Mattsson et al. [24] found in a study on biopsies sampled from oral lichen planus lesions that cells positive for TCR Vα 2 and Vβ 3 occur in higher frequencies in the lesions than in the peripheral blood. Nakajima et al. [25] reported that adult periodontitis lesions exhibit varying frequencies of cells positive for TCR V gene markers and that the TCR V gene repertoire in the lesions differs from that in the peripheral blood.

Systemic and local host response characteristics

In a recent study [26], clinical and microbiological characteristics and local and systemic immunological features, including the expression of some α/β TCR gene products, of subjects with advanced destructive periodontal disease were described. Briefly, 21 individuals with advanced periodontal disease (diseased group) and 16 age- and sex-matched healthy subjects (healthy group) were recruited. Following a clinical examination of the diseased group, the three deepest interproximal sites in the maxillary and mandibular premolar or molar segments (i.e. 12 sites in each individual) were selected for further analysis. Samples from

the subgingival microbiota were obtained from the pocket of the selected sites and prepared for microbiological examination. The gingival tissue at one of the selected sites was also biopsied. Each excised soft tissue specimen was divided into two equal portions. One portion of the biopsy was prepared for histometric and morphometric analyses. The second portion was snap-frozen and prepared for immunohistochemical analysis. A sample of peripheral blood was obtained from each individual of the diseased and the healthy groups and prepared for immunohistochemical analysis.

The selected sites of the diseased group harboured varying numbers of micro-organisms that are associated with periodontal disease. The excised gingival tissue contained inflammatory lesions with substantial numbers of lymphocytes and plasma cells including T cells and B cells and a TCR Vα/β gene repertoire dominated by Vβ 17. The TCR profile of the lesion, however, differed markedly from that of the circulating blood of the diseased subjects. While only minor differences were observed between the blood samples of the diseased and the healthy subjects regarding the TCR genes, cells positive for CD5, HLA-DR, and CD5+CD19 (autoreactive B cells) occurred in higher proportions in the blood samples of the subjects susceptible to periodontal disease than in the healthy controls.

Conclusion: TCR Vα/Vβ expression in peripheral blood samples of subjects with periodontal disease does not differ from that of healthy individuals and the periodontitis lesion expresses a unique TCR repertoire in which the Vβ 17 gene dominates.

Host response and periodontal therapy

The effect of periodontal therapy on the host response has been described previously [27–33]. While the majority of the studies referred to had restricted their host response parameters to serum antibody levels of putative periodontal pathogens, only a few reports exist concerning histological aspects of the periodontal tissue reaction to periodontal therapy. Jully et al. [27] suggest in a histological study in humans that inflammatory infiltrates remain in gingival tissues following subgingival scaling and root planing and that these infiltrates differ from an infiltrate in an untreated site.

In order to study the effect of non-surgical periodontal therapy on local and systemic host defence characteristics further, Berglundh et al. [34] recruited 16 individuals with advanced peri-

odontal disease. A baseline examination included assessment of clinical, radiographic, microbiological, and histopathological characteristics of periodontal disease as reported above [26]. Periodontal therapy, including oral hygiene instruction and subgingival scaling and root planing was performed. Re-examinations regarding the clinical parameters were performed, the subgingival microbiota harvested, and gingival biopsies collected at 12 and 24 months from the selected sites. Samples of peripheral blood were obtained from the subjects at baseline and at the 24-month re-examination.

It was demonstrated that non-surgical periodontal therapy effectively reduces symptoms such as gingivitis and probing pocket depth in the subject sample and improves the overall probing attachment level. The treatment also markedly reduced the total number of micro-organisms present in selected gingival pockets as well as the relative proportions of *A. actinomycetemcomitans, P. gingivalis,* and *P. intermedia* of the subgingival microbiota. The improved clinical condition was, in addition, accompanied by a substantial reduction in the size of the inflammatory lesion. Qualitative alterations also occurred in the lesions. Hence, following therapy both the density of B cells (CD19) and the proportion of T cells (CD3) expressing certain TCR Vβ genes were reduced in the ICT, while the overall relative number of T cells (CD3) remained unchanged. The distribution of TCR Vβ genes and lymphocyte subpopulations in the peripheral blood samples at baseline was similar to that obtained at the 24-month re-examination.

Conclusion: Non-surgical periodontal therapy markedly changes the size and composition of the plaque-associated lesion in the gingival tissue but apparently fails to affect the relative distribution of lymphocyte subsets in peripheral blood.

The two studies cited above demonstrated that TCR Vβ gene expression is unique for the periodontitis lesion and differs from that of circulating blood and that T cells will preferably occupy a small "resting" lesion in the gingival tissue after successful therapy. The fact that lymphocytes of the memory (CD45RO) phenotype [16, 17] dominate in the periodontitis lesion lends support to the hypothesis that immunocompetent cells constantly immigrate into the target (periodontitis) sites. Obviously, the periodontitis-associated lymph nodes contain lymphocytes that will proliferate and "home" back to the periodontium through the bloodstream

after stimulation. In this respect, it is interesting to analyse the edentulous and presumptive implant situation in the periodontitis-susceptible individual. Thus, the loss of teeth including the periodontitis sites, i.e. the pocket and the associated gingival lesion, may not necessarily mean that susceptibility ceases to exist. On the contrary, the lymph nodes will still contain memory cells that upon stimulation may proliferate and subsequently "home" back to the target (implant) site. To test this hypothesis, information regarding the function of the edentulous ridge mucosa and the peri-implant mucosa is required.

Immune competence of the edentulous ridge mucosa

Liljenberg et al. [35] studied some tissue characteristics of the ridge mucosa before and after implant installation. Nine partially edentulous patients were included in the study. They had all been treated for periodontal disease and were scheduled for implant therapy. The proposed implant sites had been edentulous for periods ranging between 1 and 5 years. At the time of fixture installation one recipient site in each patient was selected for soft tissue biopsy. Abutment connection and restorative therapy were performed after 3–6 months. When the implants had been in function for about 6 months, a soft tissue sample was obtained from the keratinized peri-implant mucosa at the implant site from which the first biopsy was obtained. Each biopsy was divided into a mesial and a distal portion. The mesial tissue portion was prepared for histometric and morphometric analyses, and the distal portion was snap-frozen in liquid nitrogen, stored in a freezer at $-70°$ C and subsequently exposed to immunohistochemical analysis.

Both tissues harboured a well keratinized oral epithelium and a connective tissue, the composition of which was similar with respect to collagen, cells and vascular structures. The peri-implant mucosa, however, also included a junctional epithelium which apparently allowed antigenic challenge of products from the oral cavity. As a consequence, the peri-implant mucosa, in comparison with the ridge mucosa, was found to contain significantly enhanced numbers of different inflammatory cells such as T cells (CD3), T-helper cells (CD4) and T-cytotoxic cells (CD8). While B cells (CD19) occurred in low numbers in the peri-implant mucosa, they were virtually absent in the ridge mucosa. The CD45RO (memory) phenotype and the CD45RA (naive) phenotype were also present in larger numbers in the mucosa around implants than in the ridge mucosa.

Conclusion: The keratinized mucosa of the edentulous ridge harbours inflammatory cells which express markers for various forms of immune competence. When this mucosa is penetrated by a titanium implant, a junctional epithelium forms to the abutment surface. This epithelium allows the antigenic challenge of products from the oral cavity, a phenomenon which leads to a local defence mechanism, i.e. the establishment of an infiltrate with the characteristics of a T-cell lesion.

The gingiva and the peri-implant mucosa

Animal experiments have demonstrated that the gingiva at teeth and the peri-implant mucosa have some structural features in common [36, 37]. Obvious differences also exist between the two tissues, however, particularly with respect to the morphology of the connective tissue. There are few reports regarding the function, including immune competence, of the two tissues [38, 39]. Liljenberg et al. [40] reported on characteristics of plaque-associated lesions in the gingiva and the adjacent peri-implant mucosa sampled from the same subjects. In this study, 20 partially edentulous patients volunteered to participate. They had all been treated for moderate or advanced periodontal disease. This treatment included plaque control, pocket elimination procedures, and extractions. Edentulous regions were subsequently restored with implants according to standardised procedures. The restorative therapy was completed 6–24 months before soft tissue biopsy. Samples of gingival tissue and peri-implant mucosa from an "interproximal surface" of one tooth site and one implant site in the same jaw were harvested. One portion of the biopsy was embedded in plastic and used for histometric and morphometric analyses. The second portion of the biopsy was snap-frozen in liquid nitrogen and prepared for immunohistochemical analysis.

Small inflammatory infiltrates (ICT) were found in the connective tissue lateral to the junctional epithelium in both types of tissues. The ICT of peri-implant mucosa occupied on average 0.17 mm^2 of the soft tissue, while the size of the corresponding lesion in the gingiva was 0.25 mm^2. The density of B cells (CD19) was seven times higher in the gingiva than in the peri-implant mucosa (3.7% vs. 0.5%) while the densities of T cells (CD3) were 7.5% (gingiva) and 4.7% (peri-implant mucosa), respectively. The density of elastase-positive PMN cells was about three times higher in the gingiva than in the peri-implant

mucosa. The ratio between memory (CD45RO) and naive (CD45RA) phenotypes was similar in the two types of tissues.

Conclusion: Some leukocytes occur in higher proportions in the gingiva than in the peri-implant mucosa. Care must be exercised when these differences are interpreted. First of all, the peri-implant mucosa unit – in this respect – was a relative "newcomer". Thus, while the tooth/gingiva interface had been in existence for many years, the implant/mucosa interface was relatively young, 6–24 months. It is possible that prolonged exposure of the implant site to the oral environment may induce both qualitative and quantitative changes in the infiltrate in the mucosa around the implant.

The findings reported above indicate that in peri-odontitis-susceptible subjects, the periimplant mucosa contains areas of inflammatory cell infil-trates, despite the absence of overt clinical signs of inflammation. A similar observation was made by Tonetti et al. [39] using immunohistochemical techniques on human biopsy material. Non-invasive techniques, such as analysis of crevicular fluid from tooth and implant sites, were used by, for example Adonogianaki et al. [41]. They sam-pled crevicular fluid from healthy gingival and peri-implant mucosal sites in 31 partially edentulous subjects who had at least two osseo-integrated implants. The authors reported that the volume as well as the composition of the fluid that could be harvested from the tooth (GCF) and implant (PICF) sites was similar. Adonogianaki et al. [41] suggested that "great similarities exist in the profile of GCF and PICF constituents and analogous mechanisms seem to control the inflammatory and immune responses around both implants and natural teeth".

The peri-implantitis lesion

The nature of the peri-implantitis lesion has been explored in numerous animal experiments [42–46] but very few reports exist on human biopsy material. One obvious reason for this discrepancy may be difficulties in biopsy sampling in patients with peri-implantitis due to technical and/or ethical problems. Another explanation may be that true peri-implantitis lesions are rare and, when present, difficult to detect. Accessibility for inspection of soft tissues may be compromised by suprastructures and recent information from radiographs may not be available. In the literature, there seem to be varying opinions about peri-implantitis as a disease entity, and implant failure

has been used as a criterion to be associated with either overload or infection (i.e. peri-implantitis). In a recent review on biological factors related to implant failures, Esposito et al. [47] described implant loss related to peri-implantitis. Although failures occurred with similar frequency in studies using different implant systems (Brånemark system: 104 out of 1600, and ITI system: 129 out of 1407), the authors suggested that peri-implantitis accounted for only 2.8% of the implant failures reported for the Brånemark system whereas the corresponding figure for the ITI system was 48.9%. The reason for this proposed discrepancy between the two systems is currently not understood. It should be emphasised, however,

Figure 2a. Clinical photograph of two implant sites in the right side of the maxilla.Note the swelling at the distal implant.
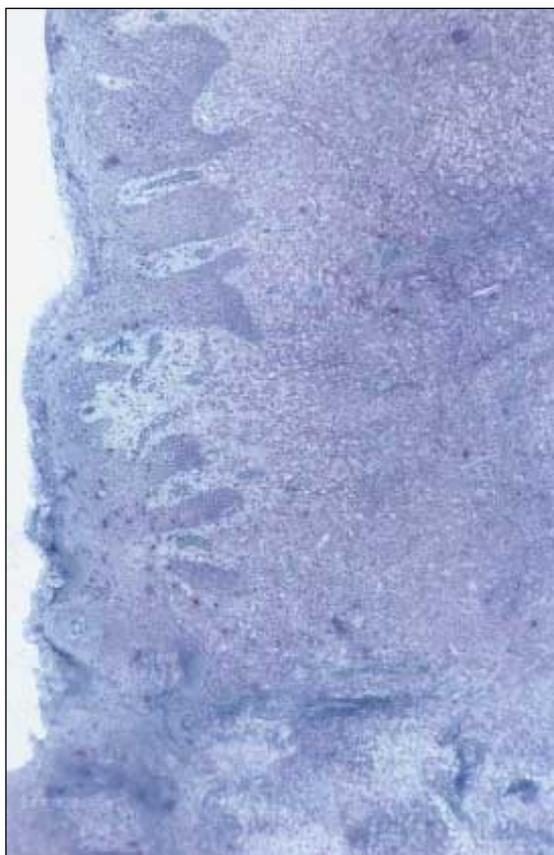

Figure 2b. Radiograph of the two implant sites illustrated in Figure 2a. Although considerable bone loss was observed at the distal implant, the fixture was found to be stable, indicating preserved osseointegra-tion in the "apical" remaining bone support when treatment of the surrounding lesion was performed.

that comparisons between different clinical studies should be made with care, due to variations in criteria and examination techniques. On the other hand, in a multicentre study by van Steenberge et al. [48] on 558 implants in 159 patients, it was reported that 2% of the implants failed during the second and third year of monitoring and that such failures occurred more frequently in subjects with a high degree of plaque accumulation.

Peri-implantitis is a condition that, if left untreated, may lead to implant failure. The diagnosis, however, is valid while the implant still remains in function. According to the *1st European Workshop on Periodontology* [49], peri-implantitis is defined as the "term for inflammatory reactions with loss of supporting bone in the tissues surrounding a functioning implant". As indicated above, most information regarding peri-implantitis has been collected from animal experiments. Consequently, the histopathological features of the peri-implantitis lesion in humans remain to be described. Biopsies may be harvested from sites where treatment of peri-implantitis is planned (Fig. 2) or where implants, due to the extent of bone loss, are scheduled to be removed. Based on the evidence from animal experiments, the remaining implant at the peri-implantitis site should be stable and demonstrate preserved osseointegration in the apical part of the fixture. Soft tissue biopsies from such sites and processed for light microscopy reveal morphological characteristics of inflammatory lesions. Figure 3 illustrates a biopsy obtained from a human implant site with peri-implantitis. The illustrated lesion is about 7 mm^2 in size and appears to be crammed with leukocytes. Early results from morphometric analyses of biopsies from patients with peri-implantitis indicate that plasma cells and lymphocytes are present in high numbers. This observation is consistent with the findings reported above for periodontitis lesions. In the peri-implantitis lesion of the present biopsy material, however, numerous PMN cells were found in perivascular connective tissue compartments distant from the pocket epithelium. This finding is not in agreement with the histopathological features of periodontal disease. The reason for this difference regarding the PMN cells and the fact that the overall density of inflammatory cells was more pronounced and the size of the lesion larger in peri-implantitis than in periodontitis is currently not understood. Additional information regarding the inflammatory infiltrate in peri-implantitis, including assessment of immune regulation as reported above, is required.

Figure 3. Mesio-distal section of a human peri-implantitis lesion. The implant has been situated to the left. A pocket epithelium is separating the "pocket" compartment from the extensive inflammatory infiltrate in the peri-implant mucosa. The infiltrate is dominated by leukocytes, such as plasma cells, lymphocytes, PMN cells and macrophages, and comparatively small proportions of collagen and vascular structures are identified.

Prognosis of implant therapy in the periodontitis-susceptible individual

Limited information exists regarding the prognosis of implant therapy in periodontally compromised dentitions. Despite anatomical problems for implant placement, such as extensive resorption of the alveolar crest prior to implant therapy, the propensity to marginal bone loss in the partially edentulous periodontitis-susceptible patient has also been discussed. Results reported by, for example Nevins and Langer [50] and Ellegaard et al. [51], however, indicate that periodontitis-susceptible individuals may also be successfully treated with dental implants. Although the observation times varied between the studies, 1–8 years and 3–5 years, respectively, it was concluded that the previous concept of contraindication for implant therapy in periodontitis-susceptible individuals may not be valid.

Mean values of marginal bone alterations over time in groups of individuals may not be suitable for discriminating changes at individual implant sites. Irrespective of the history of the patient with regard to periodontal disease, the diagnostic criteria for peri-implantitis need to be better understood. Consequently, the incidence of peri-implantitis must be more accurately described

and the correlation to periodontitis susceptibility further investigated.

Summary

The susceptible individual in periodontal and implant treatment

Advanced forms of periodontal disease affect only a small portion of an adult population. It has been suggested that such susceptible individuals express an impaired host response to the bacterial challenge. The present review reports on local and systemic immunological features in a group of subjects exhibiting advanced periodontal disease. Changes in immunological parameters after successful periodontal therapy are outlined. The propensity for the development of plaque-associated lesions in the tissue surrounding dental implants is discussed and some histopathological features of human peri-implantitis lesions are described.

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