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Do mucositis *lesions* around implants differ from gingivitis *lesions* around teeth?

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Abstract

Background: The purpose of this review was to compare peri-implant mucositis and gingivitis with respect to the pathogenesis aspects.

Search strategy: An electronic search was performed up to June 2010 based on the *PubMed* database of the National Library of Medicine and *The Cochrane Library* of the Cochrane Collaboration (CENTRAL). A hand search considered the bibliography of a recently published review on the same topic (Heitz-Mayfield & Lang 2010).

Results: The host response to biofilms does not differ substantially at teeth or implants. The most obvious sign clinically is the development of an inflammatory lesion as a result of the bacterial challenge. Gingivitis at teeth or peri-implant mucositis at implants are precursors for more detrimental lesions, and hence have to be diagnosed properly and prevented by applying anti-infective therapy. Non-surgical interventions are usually sufficient for the treatment of both gingivitis and mucositis.

Conclusions: Gingivitis and peri-implant mucositis are not fundamentally different from pathogenesis and diagnosis points of view.

Key words: aetiology; clinical parameters; gingivitis; oral implants; pathogenesis; peri-implant mucositis

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In the Sixth European Workshop on Periodontology (Zitzmann & Berglundh 2008), the definitions of peri-implant diseases have been revised: *Peri-implant mucositis* is the presence of inflammation in the mucosa at an implant with no signs of loss of supporting bone. *Peri-implantitis* in addition to inflammation in the mucosa is characterized by loss of supporting bone (Lindhe & Meyle 2008).

Most recently, a narrative review addressed the biology of chronic and aggressive periodontitis in comparison with that of peri-implantitis (Heitz-Mayfield & Lang 2010), while the present review focused on the early signs of pathology in the two soft tissue compartments adjacent to teeth or implants.

For this purpose, *peri-implant mucositis* is compared with its counterpart around teeth, i.e. *gingivitis* without any consideration of the classification of gingivitis (chronic and acute). However, it is evident that only plaque-induced gingivitis is addressed in the present comparison.

The question therefore arises – ''Is peri-implant mucositis fundamentally different from gingivitis with respect to, the pathogenesis aspects?''

Conflict of interest and source of funding statement

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Material and Methods

Search strategy

In order to obtain available data of interest, the *PubMed* database of the United States: National Library of Medicine and *The Cochrane Library* of the Cochrane Collaboration (CENTRAL) served as electronic databases. A literature search was carried out on articles published up to and including June 2010.

The key words used in this search were:

(Peri-implant mucositis OR Periimplant mucositis OR peri implant mucositis OR Mucositis OR Periimplantitis OR peri-implantitis OR peri implantitis OR periimplant OR periimplant lesions OR peri-implant lesions)

AND (Gingivitis OR gingival inflammation OR gingival host response).

During the search in the *PubMed* database, the following limits were applied:

1. Language; English and German language
2. Type of article; Clinical Trial, Controlled Clinical Trial, Case series study,

This search revealed 127 titles.

Titles and abstracts were searched in order to find papers eligible for the

review. After screening, nine were included in this review. Furthermore, the bibliography of the recently published manuscript on the same issue (Heitz-Mayfield & Lang 2010) was scanned and included where appropriate.

Only studies using some or all the indicators identified by the existing literature as correct for identifying peri-implant mucositis were included (Heitz-Mayfield 2008a,b).

Host Response Around Teeth

Biofilm development starts in the niche created where the gingival margin meets the tooth surface and is located adjacent to the non-keratinized crevice epithelium. The bacteria have to exert their effect from this *juxta* position. In some instances, the microorganisms may even invade the tissues. In either case, tissue destruction will occur – in part – as a direct result of microbial action through their release of toxins, lipopolysaccharides or enzymes, or – to a major other part – indirectly, as a result of activation of the patient's cellular and inflammatory systems – the so-called host responses, which may serve to both damage and protect the periodontal tissues (for a review, see Kinane et al. 2008).

Although no one has directly observed the earliest stages of gingivitis development in humans, it is anticipated that these include processes characteristic of acute inflammation:

- transudation of serum through the vascular endothelium
- extravasation of leucocytes and their outward emigration
- widening of the inter-cellular spaces of the surface epithelia
- gradual release of immuno-inflammatory mediators with a variety of potentials, such as cytokines (IL-1α, ILβ, IL-6, IL-8 and TNFα)

These and others have proven their effects on signalling gene expression, mobilizing of inflammatory cells in mediating the release of enzymes like collagenases, other proteolytic enzymes, including the metallo-proteinases, which are responsible for the degradation, and the extracellular matrix of the connective tissue. Moreover, these in turn give rise to potent products, such as prostaglandins, particularly PGE_2 and others that are involved in several inflammatory processes during the progression of the disease.

Also, during the early stages of the process, various bacterial antigens will elicit the production of antibodies, mobilize the complement system and release other immuno-globulins along with the emergence of phagocytic cells and activation of other cell types such as lymphocytes and macrophages. As these complex processes pervade the marginal gingiva, the developing gingival lesion matures into chronic gingivitis with massive accumulations of cells and fluid overtaking the connective tissues stroma (Fig. 1).

Host Response Around Implants

Animal experiments

The host response to biofilm formation was evaluated in a dog model

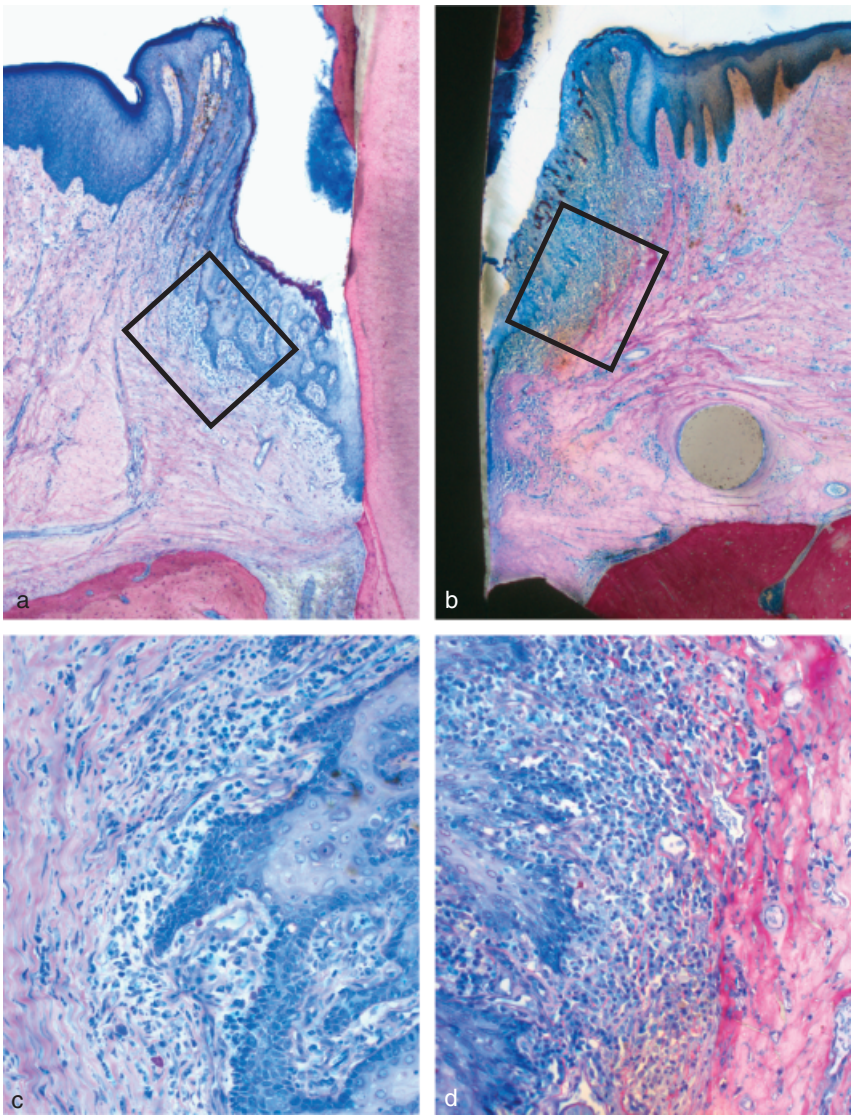

Fig. 1. Histological preparation of a gingivitis lesion in comparison with a mucositis lesion. (a) Inflammatory infiltrate as a result of the host response against the bacterial challenge. Biofilm on the tooth surface: blue, on top of calculus deposits: red. Frame enlarged in (c). (b) Inflammatory infiltrate as a result of the host response against the bacterial challenge leading to peri-implant mucositis. Biofilm on the surface of an implant: blue, on top of calculus deposits: red. Frame enlarged in (d). Heavy infiltrate, but no loss of supporting bone. (c) Higher magnification of the inflammatory infiltrate of the gingivitis lesion in (a). Massive epithelial proliferation into the collagen-reduced inflammatory infiltrate. Predominance of lymphocytes, some polymorphonuclear leucocytes. Sparse inflammatory cells in the adjacent, collagen-rich connective tissue. (d) Higher magnification of the inflammatory infiltrate of the peri-implant mucositis lesion in (b). Marked epithelial proliferation into the collagen-reduced inflammatory infiltrate. Predominance of lymphocytes. Sparse inflammatory cells in the adjacent, collagen-rich connective tissue. Very similar appearance in comparison with (c).

Table 1. Animal experimental mucositis studies

Author (year)	Number of animals	Study design	Methods	Major findings
Berglundh et al. (1992)	Five Beagle dogs, 5 months old; Brånemark implants	*De novo* plaque formation for 21 days	Clinical indices Biopsies at tooth and implant sites	Size and composition of the infiltrate identical after 3 weeks of plaque accumulation
Ericsson et al. (1992)	Five Beagle dogs, 5 months old; Brånemark implants	*De novo* plaque formation for 3 months	Clinical indices Biopsies at tooth and implant sites	Both G and PIM units yielded an inflammatory infiltrate: extension of the infiltrate more pronounced at PIM than at G sites. Composition of both G and PIM very similar
Ericsson et al. (1995)	Five Labrador dogs	Plaque accumulation up to 9 months	Clinical indices Biopsies at tooth and implant sites	Both G and PIM units yielded an inflammatory infiltrate: Extension of the infiltrate more pronounced at PIM than at G sites. Composition of both G and PIM very similar. Without plaque accumulation, no inflammatory infiltrate
Abrahamsson et al. (1998)	Five Beagle dogs with Astra Tech®, Brånemark and Straumann® implants	Plaque formation for 5 months after healing	Clinical indices Biopsies at implant sites	Establishment of an inflammatory infiltrate at all three implant systems. No difference in composition of the infiltrate. Vertical extension of ICT within 91–99% of the junctional epithelium. No difference between systems
Schou et al. (2002)	Eight cynomolgus monkeys, Astra Tech® implants	Healthy mucosa *versus* gingiva; mucositis *versus* gingivitis	Biopsies at tooth and implant sites	No systematic differences in clinical and histological estimates of the distance between the mucosal/gingival margin and probe tip. Mild marginal inflammation was associated with deeper probe penetration at implants *versus* teeth

(Berglundh et al. 1992) clinically as well as histologically following *de novo* plaque formation around teeth and implants. After 3 weeks of undisturbed plaque accumulation, the size and extent of the sub-epithelial connective tissue infiltrate was assessed. Both parameters as well as their cellular composition were identical in the gingiva and the peri-implant mucosa. This suggested that the early host response to the bacterial challenge around the implanto-mucosal unit is of a magnitude and intensity similar to that of the dentogingival unit (Table 1).

The effects of 3 months of biofilm accumulation were studied experimentally with respect to the host response with both clinical and histological parameters comparing gingival with peri-implant mucosal tissues (Ericsson et al. 1992). After 90 days of undisturbed biofilm formation, the dogs had accumulated large amounts of plaque, and the soft tissues at implants and teeth bled on gentle probing. The histological examination of the two inflamed soft tissues revealed that (a) both gingiva and peri-implant mucosa contained an inflammatory cell infiltrate subjacent to the junctional epithelium and (b) the composition of these infiltrates was similar in both gingiva and peri-implant mucosa with a substantial loss of collagen and a significant increase in inflammatory cells. However, the apical extension of the inflammatory infiltrate as well as the size of the lesion were significantly greater (almost threefold) than that in the gingiva. This host response to the bacterial challenge after a period of 3 months appeared to be more pronounced in the peri-implant mucosa than in the gingiva. However, it remains unknown whether this fact will render the peri-implant mucosal tissue more prone to the loss of supporting bone, i.e. the transition to peri-implantitis (Table 1).

The above-mentioned host response has been demonstrated to develop irrespective of the implant system used (Abrahamsson et al. 1998). Hence, it has to be realized that these defence mechanisms are not system-specific, but represent the result of the response to the bacterial challenge at any implant system (Table 1).

Comparison Between Gingivitis and Peri-Implant Mucositis Lesions in Humans

Human histological, cross-sectional studies

Although the junctional epithelium of the gingival sulcus transformed from the reduced enamel epithelium (Schroeder & Listgarten 1977), while the barrier epithelium of the peri-implant sulcus is the result of a proliferation of epithelial cells from oral epithelium, it has to be realized that despite this phenotype change, the soft tissue seal around implants is phenotypically indistinguishable from that of the dent-gingival unit (Mackenzie & Tonetti 1995) and hence is fully functionally adapted to cope with the bacterial challenge (Bosshardt & Lang 2005). This is also reflected in the fact that early inflammatory mediators, such as plasminogen activator, are equally expressed by the junctional epithelia of peri-implant mucosa or gingiva (Schmid et al. 1992).

Moreover, a necessary step for leucocyte extravasation and subsequent migration to the sites of inflammation in the initial stages of the host response to the bacterial challenge appears to be the expression of vascular cell adhesion molecules by capillary loops. The expression of such adhesion molecules in the microvasculature of gingival and peri-implant mucosal tissues was studied in human biopsies of sites clinically characterized as being healthy or slightly inflamed (Tonetti et al. 1994). No significant differences in the intensity of the expression of inter-cellular adhesive molecule-1 (ICAM-1) and other adhesive molecules, such as ELAM-1, VCAM-1 and PECAM-1, were found in the gingival and peri-implant mucosal tissues, respectively. The establishment of a gradient of ICAM-1 expression within the junctional epithelium is

thought to be an important mechanism of guiding PMNs towards the sulcus bottom, where they can control the bacterial challenge (Tonetti 1997, Tonetti et al. 1998). Obviously, these pathways are encountered both in gingiva and in peri-implant mucosa (Tonetti et al. 1994).

In characterizing the composition of plaque-induced gingival and peri-implant mucosal lesions in 20 partially edentulous patients (Liljenberg et al. 1997), the size of the inflammatory infiltrate adjacent to the lateral aspects of the junctional epithelia of the peri-implant mucosa and the gingiva did not differ significantly in the two tissues occupying 0.17 ± 0.14 and $0.25 \pm 0.21\ mm^2$, respectively. However, the numerical density of CD19-positive cells was seven times higher in the gingiva than in the peri-implant mucosa (3.7 *versus* 0.5). The numerical densities of CD3-positive cells were 7.5 and 4.7 in the gingiva and the peri-implant mucosa, respectively. Also, the numerical density of PMNB elastase-positive cells was three times higher (3.7 *versus* 1.2) in the gingiva than in the peri-implant mucosa (Liljenberg et al. 1997).

Because this biopsy material was cross-sectional in nature, the accurate duration of the bacterial challenge was not known, and hence it may be speculated that a prolonged exposure of the implant site to the oral environment may result in both quantitative and qualitative changes in the composition of the infiltrate. Consequently, the slight differences revealed in the study mentioned (Liljenberg et al. 1997) have to be interpreted with caution.

Despite the small differences (Table 2b) in the composition of the inflammatory infiltrate in the comparative cross-sectional studies, it has to be assumed that host responses developed as a result of the biofilm accumulation on teeth or implants are very similar (Fig. 1).

Human experimental studies

Only two controlled human study addressed the effect of biofilm formation on the development of the inflammatory response (Pontoriero et al. 1994, Zitzmann et al. 2001, 2002). In the first study (Pontoriero et al. 1994), 20 partially dentate patients received oral implants following the successful completion of periodontal therapy. After 6 months of closely supervised oral hygiene, the patients were asked to refrain from oral hygiene practices for a period of 3 weeks. At the end of this period, optimal plaque control was, again, reassumed. Comparison of the accumulation of biofilm and the host response expressed at gingival and peri-implant mucosal tissues revealed no difference in the development of gingivitis and mucositis, respectively (Table 1). Hence, a similar cause–effect relationship between the accumulation of biofilm and the development of peri-implant mucositis was established as for dento-gingival units presented 30 years earlier in the experimental gingivitis model (Löe et al. 1965). More recently, this cause and effect relationship has, again, been confirmed in humans (Zitzmann et al. 2001, 2002). In 12 partially dentate subjects, the inflammatory response was also characterized by the enumeration of the proportions of T and B cells in both gingival and peri-implant mucosal units. No statistically significant differences in the composition of the host response within these tissues could be demonstrated after 3 weeks of biofilm formation (Table 2a). However, it was suggested that the relative larger increase in the size of the lesion and the different cell proportions in the gingiva than in the peri-implant mucosa after 3 weeks of plaque

Table 2a. Human experimental mucositis studies

Author (year)	Number of patients	Study design	Methods	Major findings
Pontoriero et al. (1994)	10 partially edentulous patients	Experimental plaque accumulation for 21 days	Clinical indices Microbiol. parameters	PII and mod. SBI increased identically in G and PIM sites No significant difference in the shifts in morphotypes at G or PIM sites
Zitzmann et al. (2001)	12 partially edentulous patients	Experimental plaque accumulation for 21 days	Biopsies from Day 0 and 21	Increase of infiltrate Ging (G): 0.03–0.26 mm^2 Peri-impl.M: 0.03–0.14 mm^2 G: Decrease in the CD3/CD19 ratio PIM: Increase in the CD3/CD19 ratio

Table 2b. Comparative human biopsy studies

Author (year)	Number of patients	Study design	Methods	Major findings
Schmid et al. (1992)	16 biopsies from edentulous patients	Expression of plasminogen activator in inflammation	Cryostat sections Immunohistochemistry	No significant difference in the expression of PA at G or PIM sites
Mackenzie & Tonetti (1995)	Five biopsies of edentulous patients	Phenotypes of junctional epithelial cells	Differentiation patterns of cytokeratins	No significant differences in gene expression. Development of identical phenotypes
Tonetti et al. (1994)	16 biopsies from partially edentulous patients	Distribution of ICAM-1, ELAM-1, VCAM-1, PECAM-1	Three-stage immunoperoxidase technique	No differences of HEV-CAM expression in G or PIM
Liljenberg et al. (1997)	20 partially edentulous patients	Cellular composition of inflammatory infiltrate	EPON sections stained with PAS and toluidine blue 15 snap-frozen sections in cryostat	Inflammatory infiltrate: G: $0.25 \pm 0.21\ mm^2$ PIM: $0.17 \pm 0.14\ mm^2$ Numerical density of cells: CD19 positive: G:3.7; PIM:0.5 CD3 positive: G:7.5; PIM: 4.7 PMN elastase positive: G: 3.7; PIM: 1.2

accumulation could be explained by the difference in the history of exposure to the oral environment. While the implant sites were exposed to the various challenges in the oral cavity for about 2 years, the teeth had been exposed to the same challenges for more than 50 years.

Diagnostic Aspects

The earliest clinical sign of gingival inflammation is the *transudation of gingival fluid*. This thin and almost acellular transudate is gradually superceded by a fluid consisting of serum plus leucocytes.

Similar phenomena of transudation converting to exudation have been identified for the peri-implant sulcular tissues. A review of peri-implant crevicular fluid assays potential in monitoring and predicting peri-implant tissue responses has been presented by Kaklamanos & Tsalikis (2002). Recently, various components of crevicular fluid from peri-implant sulci have been identified, such as collagenase-2, MMP 8 (Kivelä-Rajamäki et al. 2003, Xu et al. 2008) soluble RANKL (Monov et al. 2006) as well as aspartate aminotransferase (Paolantonio et al. 2000) and proinflammatory mediators (Petković et al. 2010). Hence, the peri-implant sulcus represents an environment in which early inflammatory as well as tissue-breakdown phenomena may be studied.

The *redness* of the gingival margin arises partly from the *aggregation and enlargement of blood vessels* in the immediate sub-epithetial connective tissue and the loss of keratinization of the facial aspects of gingiva.

Swelling and loss of texture of the free gingiva reflect the loss of fibrous connective tissue and the semiliquidity of the inter-fibrillar substance.

Individually and collectively, the clinical symptoms of chronic gingivitis and peri-implant mucositis are rather vague and usually *painless*. These features leave most patients unaware of the disease and are generally underestimated by the dental practitioners. Chronic gingivitis rarely shows spontaneous *bleeding*. Neither do peri-implant mucositis lesions. The fact that the gingival tissues can be induced to bleed just by touching the gingival margin with a blunt instrument (as during tooth brushing or in assessing the Gingival Index) suggests that the epithelial changes and the vascular transfigurements are quite conspicuous. Again, the tendency to bleed on gentle probing (Gerber et al. 2009) represents a key feature of peri-implant mucositis. Studies have demonstrated that higher diagnostic accuracy may be attributed to bleeding on probing around implants when compared with around teeth (Luterbacher et al. 2000)

In assessing peri-implant pathology clinically, an evaluation of the inflammatory status has to be supplemented by an assessment of the possible damage to the peri-implant tissues as expressed by increased probing depth and loss of connective tissue attachment.

While the presence of inflammation may lead to the diagnosis of peri-implant mucositis, increasing probing depth measurements are highly sensitive diagnostic parameters for peri-implantitis. Conversely, the absence of increased probing depth represents peri-implant stability.

Because the pathogeneses of peri-implant mucositis and peri-implantitis closely resemble those of gingivitis and periodontitis, it is imperative to use the same diagnostic criteria for the detection of peri-implant lesions and for monitoring implant stability over time (Lang & Tonetti 1996, Heitz-Mayfield 2008a).

It has been documented that probing the peri-implant sulcus will result in the formation of a new epithelial attachment within 5 days (Etter et al. 2002) as it does when probing the periodontal sulcus (Taylor & Campbell 1972). The application of a light probing force (0.2–0.3 N) will reveal reliable assessments of probing depth also around implants (Lang et al. 1994, Schou et al. 2002, Gerber et al. 2009).

Probing depth measurements have to be related to baseline assessments of probing depth obtained after the placement of the reconstruction. In the light of the desirability of more apical placements of implants allowing for an optimal emergence profile of the crown, initial probing depth measurements may exceed the usually encountered 3–4 mm. Consequently, the development of disease will be associated with increasing probing depth from the baseline value. Nevertheless, a 6 mm peri-implant pocket was found to be indicative of peri-implantitis (Fransson et al. 2008). Consequently, peri-implant mucositis sites will be characterized by positive bleeding on probing and probing depth of <6 mm.

Conclusions

In conclusion, it is evident that gingivitis and peri-implant mucositis are not fundamentally different from the perspectives of pathogenesis. Both diseases represent a host response to the bacterial challenge caused by biofilm formation. Because peri-implant mucositis represents the obvious precursor of peri-implantitis as does gingivitis for periodontitis, treatment of mucositis has to be the pre-requisite for the prevention of peri-implantitis.

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Clinical Relevance

Scientific rationale for the study: A comparison of peri-implant mucositis and gingivitis with respect to pathogenesis aspects and diagnosis.
Principal findings: Gingivitis and peri-implant mucositis are not fundamentally different. Both diseases represent a host response to the bacterial challenge caused by biofilm formation.
Practical implications: Because peri-implant mucositis represents the obvious precurser of peri-implantitis as does gingivitis for periodontitis, treatment of mucositis has to be the pre-requisite for the prevention of peri-implantitis.