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Are peri-implantitis lesions different from periodontitis lesions?

Tord Berglundh[1], Nicola U. Zitzmann[2] and Mauro Donati[1]

[1]Department of Periodontology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [2]Clinic for Periodontology, Endodontics and Cariology, University of Basel, Basel, Switzerland

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Abstract

Aim: To compare histopathological characteristics of peri-implantitis and periodontitis lesions.

Methods: A search was conducted on publications up to July 2010. Studies carried out on human biopsy material and animal experiments were considered.

Results: While comprehensive information exists regarding histopathological characteristics of human periodontitis lesions, few studies evaluated peri-implantitis lesions in human biopsy material. Experimental peri-implantitis lesions were evaluated in 10 studies and three of the studies included comparisons to experimental periodontitis. *Human biopsy material*: the apical extension of the inflammatory cell infiltrate (ICT) was more pronounced in peri-implantitis than in periodontitis and was in most cases located apical of the pocket epithelium. Plasma cells and lymphocytes dominated among cells in both types of lesions, whereas neutrophil granulocytes and macrophages occurred in larger proportions in peri-implantitis. *Experimental studies*: placement of ligatures together with plaque formation resulted in loss of supporting tissues and large ICTs around implants and teeth. Following ligature removal, a ''self-limiting'' process occurred in the tissues around teeth with a connective tissue capsule that separated the ICT from bone, while in peri-implant tissues the ICT extended to the bone crest.

Conclusion: Despite similarities regarding clinical features and aetiology of peri-implantitis and periodontitis, critical histopathological differences exist between the two lesions.

Key words: dental implants; histology; inflammatory lesion; peri-implantitis; periodontitis

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Peri-implantitis is characterized by inflammatory lesions in peri-implant tissues and associated loss of supporting bone (Zitzmann & Berglundh 2008). While peri-implantitis and periodontitis have many clinical features in common, structural differences in supporting tissues between implants and teeth may influence host response to infection. Analysis of the two types of lesions is important in the assessment of diagnosis and in the planning of treatment protocols of peri-implantitis.

In the present review, data from studies describing histopathological characteristics of lesions analysed in human biopsy material and experimental protocols were evaluated to answer the question whether peri-implantitis lesions are different from periodontitis lesions.

Conflict of interest and source of funding statement

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Search strategy

For the purpose of retrieving information on inflammatory lesions in peri-implantitis and periodontitis, studies to be selected had to include histological assessments made on tissue samples. Thus, studies made on human biopsy material or on specimens obtained from appropriate animal experiments were considered. The *PubMed* database of the United States: National Library of Medicine and *The Cochrane Library* of the Cochrane Collaboration (CENTRAL) served as electronic databases and the search was carried out on publications up to July 2010.

Human biopsy material

In the search on studies on peri-implantitis, identified sites for analysis had to

fulfill the requirement for the definition and diagnosis of peri-implantitis (Heitz-Mayfield 2008, Zitzmann & Berglundh 2008) and, hence, present with the findings on bleeding-on-probing or other clinical signs of inflammation in the peri-implant mucosa together with loss of supporting bone. The following search terms were used; peri-implantitis, peri-implant infection, peri-implant disease, biopsy, cell phenotype, histopathology, histology, human, immunohistochemistry (IHC), inflammatory cells, inflammatory lesion, and inflammation.

In a review on adaptive host response in periodontitis performed in conjunction with the 5th EWOP (Berglundh & Donati 2005), phenotype characteristics of cells in periodontitis lesions were described. The data on cellular composition in periodontitis lesions collected up to 2005 in the review referred to were used in the current work. Thus, the additional search in the field of human periodontitis lesions included publications from 2005 and was based on the following search terms: periodontitis, periodontal disease, biopsy, cell phenotype, histology, histopathology, human, IHC, inflammatory cells, inflammatory lesion, and inflammation.

Experimental studies

The search related to experimental studies on peri-implantitis and periodontitis included publications providing histopathological data on peri-implantitis lesions. Analysis of lesions produced from experimental periodontitis was performed in studies evaluating both experimental conditions (peri-implantitis and periodontitis lesions). The search terms used in addition to those described for peri-implantitis lesions in human biopsy material were animal experiment and experimental peri-implantitis.

Results

Peri-implantitis – human biopsy material

Studies describing peri-implantitis lesions based on analysis of human biopsy material are reported in Table 1. Sanz et al. (1991) analysed biopsies obtained from six subjects with peri-implantitis. The diseased sites presented with BoP and bone loss $\geqslant 3$ mm. The histological analysis revealed that the sulcular/pocket epithelium contained transmigrating leucocytes and that an inflammatory cell infiltrate (ICT) consisting of mononuclear cells, plasma cells, and enlarged blood vessels occupied about 65% of the connective tissue portion. Cornelini et al. (2001), who analysed soft-tissue biopsies collected from 10 implant sites with radiographic bone loss, BoP and suppuration, found lymphocytes, plasma cells, and few neutrophil granulocytes in the inflammatory lesions. In a study using IHC on frozen sections prepared from peri-implantitis sites in six subjects, Gualini & Berglundh (2003) reported that the ICTs contained large proportions of CD19-positive cells (B lymphocytes) and that B cells outnumbered T cells. It was also reported that elastase-positive cells occurred in high numbers in areas located close to the pocket epithelium and also in central portions of the lesions. In contrast to the findings presented by Gualini & Berglundh (2003), Bullon et al. (2004) in a study on inflammatory lesions in peri-implantitis and periodontitis reported that both types of lesions contained T- and B lymphocytes, plasma cells, and macrophages and that T cells occurred in higher numbers than B cells. Berglundh et al. (2004) analysed semi-thin plastic-embedded sections prepared from sites with severe peri-implantitis. The pocket epithelium presented with rete ridges and was, in the apical portion, thin and ulcerated. The ICT appeared to occupy almost the entire connective tissue compartment and extended apical of the pocket epithelium. While the marginal portion of the ICT contained small vascular units and collagen fibres together with lymphocytes and plasma cells, the apical portion exhibited higher densities of lymphocytes, plasma cells, and polymorphonuclear (PMN) cells. The PMN cells were found not only in pocket epithelium-associated areas, but also in central peri-vascular compartments. Large-sized bacteria were present in the apical zone of the ICT that was facing the pocket. Berglundh et al. (2004) also reported that the average size of the peri-implantitis lesions was 3.61 mm^2 and that the morphometric/stereologic analysis revealed that plasma cells dominated among inflammatory cells in the ICT and that the proportions of PMN cells and macrophages were in relative terms high.

Konttinen et al. (2006) performed immunohistochemical analysis of soft-tissue samples representing periodontitis and peri-implantitis. It was reported that the number of cells positive for interleukin (IL-1α) and IL-6 was larger and the number of TNF-α-positive cells smaller in peri-implantitis than in periodontitis lesions.

Periodontitis – human biopsy material

Phenotype characteristics of inflammatory cells in human periodontitis lesions are reported in Tables 2a and 2b. Table 2a is modified from data presented in the review by Berglundh & Donati (2005), whereas Table 2b includes information published up to 2010. As was stated in the review by Berglundh & Donati (2005), the methods used for the identification of cells and structures changed over time and most studies published during the last 20 years applied IHC or in situ hybridization techniques. Information retrieved from such techniques together with data obtained from older studies based on assessments made on morphological criteria in the review by Berglundh & Donati (2005) revealed that B cells together with plasma cells dominated among inflammatory cells in lesions of chronic and aggressive periodontitis. While T helper cells occurred in larger numbers than T cytotoxic cells, macrophages, and neutrophil granulocytes represented $<5\%$ of the cell population in such lesions. Data from publications from 2005 to 2010 confirmed in major terms previous observations (Table 2b). Thus, Nakajima et al. (2005) and Noda et al. (2007) in studies on biopsies from 17 and 22 subjects with periodontitis, respectively, reported that B cells dominated over T cells. Similar observations were made by Donati et al. (2009). They analysed biopsies from 38 subjects with severe chronic periodontitis and found that B cells occurred in larger proportions than T cells and plasma cells. In contrast to older documentation, in which plasma cells were identified using morphological criteria, Donati et al. (2009) applied IHC and the CD138 marker. A similar technique was used by Kim et al. (2010), who reported that plasma cells dominated over T cells in periodontitis lesions.

A meta-analytic approach regarding the reported proportions of inflammatory cells in periodontitis lesions, similar to that presented in the review by Berglundh & Donati (2005), was applied for the entire data set of publications in Tables 2a and 2b. The relative distribution of inflammatory

Table 1. Peri-implantitis lesions – human biopsy material

References	Number of subjects/implants/teeth involved	Definition-diagnosis for peri-implantitis/function time/implant system	Methods	Results
Sanz et al. (1991)	Six subjects Number of implants not specified	PPD > 3 mm, BOP+, no implant mobility (periotest < +9), marginal bone loss > 3 mm, peri-implant radiolucency Implant-supported bridges had been in place for ⩾1 year Brånemark	Inter-proximal soft-tissue biopsy Histometry and transmission electron microscopy	Sulcular epithelium: proliferation, akanthosis, and papilomatosis, enlarged inter-cellular spaces, transmigrating mono- and polymorphonuclear cells ICT occupied 65.5% of the connective tissue compartment ICT: mononuclear (1148/mm^2) and plasma cells (419/mm^2) dominating, few PMNs (14/mm^2), enlarged blood vessels
Cornelini et al. (2001)	Number of subjects (non-smokers) not specified 10 implants	PPD > 5 mm, BOP+, suppuration, swelling, radiographic bone loss Implants had been in place for ⩾1 year ITI implants	Soft-tissue biopsies IHC: vascular endothelial growth factor (VEGF) and microvessel density (MVD)	ICT: lymphocytes and plasma cells, few neutrophils All vessels and most lymphocytes and neutrophils were VEGF positive
Gualini & Berglundh (2003)	Six subjects ⩾1 implant site exhibited signs of peri-implantitis (PI) Number of implants not specified	Suppuration, BOP+, no implant mobility, continuous marginal bone loss in radiographs (no probing) Implants in function for 5–11 years Brånemark	Soft-tissue biopsies IHC: CD3, CD4, CD8, CD19, elastase	Ulcerated pocket epithelium Lateral to the pocket epithelium: elastase-positive cells ICT: large proportions of B cells (CD19$^+$) and elastase-positive cells, B cells outnumbered T cells (CD3 10%, CD4 8%, CD8 6%, CD19 13%, elastase 4%)
Bullon et al. (2004)	10 subjects Five subjects with PI (five implants) Five subjects with AG (five biopsies from sites with PPD ⩾6 mm)	PPD > 5 mm, BOP+, swelling of tissues, plaque index 2, radiographic bone loss Several months loading (average not specified) Implant type not specified	Soft-tissue biopsies Histological and IHC in areas: oral epithelium (O), sulcular epitelium (S), junctional epithelium (J), supracrestal connective tissue Vascular proliferation analysed by immunoreactivity for vascular endothelial cells (CD34), factor VIII, vascular endothelial growth factor (VEGF) Apoptosis analysed by oncoproteins bcl2 and p53 immunoreactivity	O: multi-layered parakeratinized epithelium in PiM and AG sites; in PiM significantly less CD1a and CD34, but significantly more VEGF and bcl2 than in AG sites; Langerhans cells and immature DCs (CD1a) present in PiM and AG sites J: disrupted in PiM (thin non-keratinized, partly ulcerated) S–J: significantly more CD34 (almost × 2), significantly more FVIII (× 2), VEGF (× 1.5) in PiM than in AG sites ICT in PiM: granulation tissue, focally haemosiderin, B and T lymphocytes (T cells predominant) macrophages, plasma cells (inflammatory cell types similar to AG sites) bcl2 and p53 similar in PiM and AG sites
Berglundh et al. (2004)	Six subjects 12 implants	Suppuration, swelling and/or fistula formation, advanced radiographic bone loss, mobility in seven implants Implants in function for 4–21 years Brånemark	Soft-tissue biopsies Histology	Pocket epithelium: rete ridges, apical thin and ulcerated ICT: occupied almost entire CT, reached apical of the pocket epithelium ICT marginal: large numbers of collagen fibers together with numerous lymphocytes and plasma cells, numerous small vessels ICT central part: few or absent collagen fibers, few large vascular units, large numbers of plasma cells and PMNs (PMNs also in perivascular compartments distant from the implant surface), 39% plasma cells, 7% lymphocytes, 5% macrophages, 4% PMNs
Konttinen et al. (2006)	20 subjects: 10 subjects with PI (10 implants) 10 subjects with CP (number of gingiva biopsies not specified)	Pain during mastication and implant mobility and vertical bone loss Time in function not specified Implant type not specified	Soft-tissue biopsies (PiM and gingiva) IHC (TNF-α, IL-1α, IL-6, PDGF-A, TGF-α)	PiM: higher percentage of IL-1α and IL-6, lower percentage of TNF-α than in CP sites Foreign body giant cells only in PiM (originated from macrophages, produce osteoclast-stimulating cytokines), not in CP sites

PI, peri-implantitis; PiM, peri-implant mucosa; AG, aggressive periodontitis; CP, chronic periodontitis; ICT, inflammatory cell infiltrate in the connective tissue; CT, connective tissue; PPD, probing pocket depth; PAL, porbing attachment level; BoP, bleeding-on-probing; PMN, polymorphonuclear cells; IHC, immuno-histochemistry.

Table 2a. Periodontitis lesions – human biopsy material (from Berglundh & Donati 2005)

Reference	Periodontal diagnosis	Sample	Technique	Results
Mackler et al. (1977)	Five patients of various age and sex	Gingival biopsies from periodontitis subjects	Immunofluorescence	Higher concentration of lymphocytes and plasma cells (IgG and IgM) in periodontitis biopsies compared with normal healthy biopsies
Seymour & Greenspan (1979)	Patients with chronic periodontal disease	Twelve biopsies. Sites scheduled for surgery with PPD 4–8 mm and BoP+	IHC, immunofluorescence	Majority of the lymphocytes had the phenotype of B cells and were positive for IgM and IgG
Lindhe et al. (1980)	Twenty-two patients with advanced periodontal tissue destruction, with PPD $\geqslant$ 8 and 50% bone loss	In each patient, six sites were selected representing advanced disease, established gingivitis and ''healthy'' gingival	Morphometric analysis. Numerical density (N_v) and volumetric density (V_v) of cells.	Periodontitis lesion: 31% plasma cells, 5–10% lymphocytes, 5% fibroblast, 1.3% macrophages, 1.3 Neutrophils G., 11% collagen In the gingivitis lesion, the ratio lymphocytes-plasma cells was 1:1, in the periodontitis was 1:3
Liljenberg & Lindhe (1980)	Seven adult periodontitis	Biopsies from diseased sites with PPD>8 mm, and >50% of bone lost	Morphometric analysis	The ICT of all gingival units of patients was characterized by high plasma cell density; between 56.8% and 84% of all cells were plasma cells
Charon et al. (1981)	Fifteen patients 30–88 years old with advanced periodontal disease	Biopsies from both diseased and healthy sites	IHC	The plasma cell dominated in the periodontitis lesion. The presence of T cells and activated macrophages indicated that both humoral and cell-mediated responses are operative in human chronic periodontitis
Okada et al. (1983)	Patients with advanced periodontitis (29–55 years of age)	Biopsies from sites with PPD $\geqslant$ 5 mm and evidence of bone destruction	IHC	Only few PMNs were observed. Plasma cells predominated in the central portion of the lamina propria, with the proportions positive for IgG, IgA and IgM accounting for 65.2%, 11.2% and 1.3% of the total infiltrating cells
Gillett et al. (1986)	Chronic adult periodontitis	12 chronic adult periodontitis	IHC	Lesions in chronic adult periodontitis were dominated by lymphocytes HLADr+ (B cells) and plasma cells
Passo et al. (1988)	Advanced chronic periodontitis patients (9)	33 bleeding suppurating (S) and 23 bleeding non-suppurating (NS) inter-proximal biopsies	IHC and morphometric analysis	In both suppurating (S) and non-suppurating (NS) biopsies, plasma cells and lymphocytes dominated. The vast majority of T cells were of T helper, with few T cytotoxic/suppressor cells
Reinhardt et al. (1988)	Thirteen adult periodontal maintenance patients	Biopsies from ''active'' sites ($\geqslant$ 2 mm clinical attachment loss within 3 months of biopsy) and clinically similar but ''stable'' or healthy sites	IHC	Pan B cells were significantly more prevalent in infiltrates from active sites than in stable ($p < 0.05$) or healthy ($p < 0.01$) sites. The T/B cell ratio was also significantly lower in active than stable biopsies ($p < 0.05$)
Cobb et al. (1989)	Chronic adult periodontitis	Chronic periodontitis: PI < 1.0, GI at least 2.0, PPD $\geqslant$ 6 mm	IHC	The T- and B lymphocyte populations increased approximately 20 × progressing from healthy to gingivitis to periodontitis specimens, the NK cell population showed only a 3 × increase, which represented 19%, 6.6% and 7% of the total of all positively stained lymphocytes across biopsy groups
Joachim et al. (1990)	Biopsies from 20 patients and three control volunteers	Five with treated adult periodontitis (AP), five with untreated AP	Electron microscopy and quantification of plasma cells by ultra-structural classification	Plasma cell (PC) counts increased significantly with lesion severity
Zappa et al. (1991)	10 adult patients with untreated advanced periodontitis were monitored during a period of 10 months	Using an electronic pressure-sensitive probe sites were identified which had $\geqslant$ 2 mm attachment loss within the previous month (P) and non-progressive sites (C)	Light microscopic evaluation of nuclear and cytoplasmatic staining	In P sites, the numbers of macrophages, plasma cells, lymphocytes and total inflammatory cells were significantly higher as compared with C sites. There were no differences in cell populations between superficial and deep connective tissue areas within P and C sites.

Table 2a. (Contd.)

Reference	Periodontal diagnosis	Sample	Technique	Results
Gemmell et al. (1992)	26 adult periodontitis patients (AP)	Peripheral blood and gingival biopsies	Two-color immunofluorescence, flow cytometry	The proportion $CD45RA^+$ CD4 cells was 22% in AP
Yamazaki et al. (1993)	Patients with moderate-to-advanced adult periodontitis (19)	Periodontitis biopsies with varying degree of inflammation (GI of 0–2) PPD >4 mm and CAL >5 mm	IHC	The percentage of $CD23^+$ and $CD25^+$, $CD19^+$ B cells, which were identified in 13 out of 19 samples from periodontitis, varied significantly in spite of similar clinical status
Liljenberg et al. (1994)	Eight subjects (test) with advanced periodontal disease, with >2 mm of attachment loss at $\geqslant 3$ sites in a 12-month interval	Test subjects; biopsies from progressive disease active (PDA) and progressive disease inactive (PDI) sites	Morphometric analysis of the ICT and IHC	The progressive disease sites (PD) were comprised of a larger volume of plasma cells, a higher percentage number of macrophages and lower numerical density of lymphocytes than the (NPD) group. Both T cell markers (CD3 and CD4) and B cells markers (CD22) were significantly elevated in the PDA compared with the PDI lesions
Berglundh et al. (1998)	Advanced adult periodontitis (21 subjects)	Gingival biopsies from AP groups	IHC and flow cytometry	Similar proportions of T- and B cells in gingival biopsies obtained from 21 subjects with advanced periodontitis
Orima et al. (1999)	Fourteen patients with moderate-to-advanced adult periodontitis	Sixteen biopsies PPD = 7.8 ± 2.8; CAL = 9.6 ± 2.6 BL(%) = 84.7 ± 16.3; Bop(n) = 14/16	IHC	While most T- and B cells expressed CD28, and CD80 and CD86 in gingival tissues, the expression of CD40L and CTLA-4 was lower and highly variable between specimens. The distribution of $CD40^+$ cells was similar to that of $CD19^+$ cells. The percentage of $CD40^+$ cells in the $CD19^+$ cells was nearly 100%
Berglundh et al. (1999)	16 individuals with advanced periodontal	Biopsies before and at 12 and 24 months after periodontal therapy (SRP). Peripheral blood obtained from the subjects at the 24-month re-examination	IHC and flow cytometry	Improved clinical condition following SRP was accompanied by a substantial reduction of the size of the ICT. Following therapy, the densities of CD19 and CD3 positive cells and cells expressing TCR V β genes were reduced in the ICT. But the relative distribution of lymphocyte subsets in peripheral blood was unchanged
Lappin et al. (1999)	Nine patients with adult periodontitis (AP)	Biopsies form AP (9)	IHC	A greater number of B cells were observed in the diseased than in the healthy tissues
Berglundh et al. (2001)	21 adults with advanced adult periodontitis (AP group)	Gingival biopsies and peripheral blood samples obtained from all in the AP group	Morphometric analysis and IHC	The ICT contained a large proportion of lymphocytes and, in particular B cells, in the AP group
Gemmell et al. (2001)	26 periodontitis subjects	Biopsies from moderate-to-advanced disease (PPD >4 mm). The samples were grouped according to the size of the infiltrate	IHC	A higher percentage of $CD86^+$ cells indicated predominance of Th2 response in periodontitis tissues. The analysis of revealed that CD80 was expressed predominantly by macrophages while both macrophages and B cells expressed CD86
Hillmann et al. (2001)	Five patients with adult periodontitis (AP)	Biopsies from sites with PPD 8–12 mm and alveolar bone loss $\geqslant 50\%$	Immunohistological methods	Specimens contained large proportions of plasma cells and B cells
Gemmell et al. (2001)	25 periodontitis patients	Gingival biopsies. Group 1, small; group 2, medium; group 3, extensive infiltrates	IHC	B cells were the predominant APC in group 2 and 3 tissues. The percentage of B cells in group 3 lesions was increased in comparison with group 1 healthy tissues and also in comparison with group 3 healthy/gingivitis sections
Gemmell et al. (2002)	25 patients with moderate-to-advanced periodontitis	Biopsies. The samples were grouped according to the size of the lesion: group 1, small; group 2, medium; group 3, extensive infiltrates	IHC	Numerous $CD1a^+$ Langerhans cells in the epithelium in all groups. The percentage of $CD83^+$ dendritic cells in the ICT was higher than the percentage of $CD1a^+$, $CMRF\text{-}44^+$ or $CMRF\text{-}58^+$ dendritic cells. The percentage of

Table 2a. (Contd.)

Reference	Periodontal diagnosis	Sample	Technique	Results
				$CD14^+$ cells in the inflammatory infiltrates was similar to that of $CD83^+$ cells. B cells were the predominant APC in group 2 and 3 tissues. The percentage of B cells in group 3 periodontitis lesions was increased in comparison with group 1 periodontitis tissues
Mahanonda et al. (2002)	Six patients with generalized severe adult periodontitis	Biopsies at sites with >2/3 of the root lenght of bone loss, mobility degree III	Flow cytometry	Significant upregulation of CD86 and CD83 expression was detected in periodontitis lesions, and most of this occurred on B cells. Analysis of APC function by bacterial-activation revealed that B cells served as potent APCs in mixed leukocyte reactions and stimulated T cells to produce high levels of γ-interferon

Table 2b. Periodontitis lesions – human biopsy material

References	Objective	Gingival Sample	Technique	Results
Ambili et al. (2005)	To compare the expression of NF-κB (p50/p65) in clinically healthy and chronic periodontitis (CP) subjects	20 CP subjects	IHC	Nuclear immunoreactivity for NF-κB1 (p50) was found in 90% of test subjects and 30% of controls. A more significant result was found for NF-κB2 (p65) (75% *versus* 5%). Cytoplasmic reactivity was also more intense in test subjects compare with controls
Lu et al. (2005)	To investigate the expression patterns of b-defensin-3 (hBD-3) in human gingiva.	Biopsies from 20 chronic periodontitis subjects (CP)	IHC ISH	In CP subjects, hBD-3 expression extended from the basal layer to the spinous layers (82%), and in pocket tissues it extended to the superficial spinous layers. The hBD-3 peptide was expressed not only in gingival keratinocytes, but also in Langerhans cells and Merkel cells
Nakajima et al. (2005)	To identify $CD4^+CD25^+$ Tr cells in periodontitis tissue and compare with gingivitis tissue	Biopsies from 17 periodontitis subjects	IHC	Periodontitis lesions showed a dominance of B cells over T cells, while T cells dominated over B cells in gingivitis lesions. While the $CD4^+CD25^+$ cells were found in both type of tissue, periodontitis lesions showed significantly higher percentage
Novak et al. (2005)	To evaluate whether IgG locally produced by plasma cells displayed altered glycosylation	Biopsies from 14 periodontitis patients and 10 controls	ELISA Gas chromatography Immuno-fluorescence	It was shown that a proportion of IgG-producing cells contained galactose-deficient IgG in the cytoplasm. Gingivae from periodontal disease patients exhibited infiltration of IgG-producing plasma cells; many of them contained galactose-deficient IgG in the cytoplasm
Ren et al. (2005)	To investigate the simultaneous expression of LPS, mCD14, TLR 2, four in gingival tissue	Biopsies from 43 chronic periodontitis subjects	IHC	In periodontal diseased tissue, TRL2 was detected both in pocket epithelia and in macrophage-like cells in connective tissue, whereas TRL4 was detected in connective tissue
Bodineau et al. (2006)	To study the MMP 2 and 9 and their tissue inhibitors by Langerhans cells in healthy and diseased periodontal tissue	12 biopsies from 6 periodontitis subjects	IHC Confocal microscopy	Langerhans cells expressed MMP 2 and 9 and tissue inhibitors of MMP 1 and 2 in diseased tissues. The tissue inhibitors of MMP-positive Langerhans cells were mainly observed in the upper epithelial layers. MMP 9-positive Langerhans cells were observed especially during periodontitis and in the basal epithelial layer or crossing the basement membrane
Kawai et al. (2006)	The aim of this study was to identify the cellular source of RANKL in the bone resorptive lesions of periodontal disease	Biopsies from 32 chronic periodontitis subjects	Immunofluorescent laser scanning confocal microscopy	It was demonstrated that in diseased gingival tissues, >50% and 90% of T and B cells, respectively, expressed RANKL

Table 2b. (Contd.)

References	Objective	Gingival Sample	Technique	Results
Noda et al. (2007)	To investigate the correlation between periodontopathic bacteria and host immune cell infiltrates	Twenty-two biopsies from chronic periodontitis subjects were included in this study	IHC	The mean number of infiltrated B cells was significantly larger than that of T cells in the sites harboring both *Porphyromonas gingivalis* and *Tannerella forsythia*. Similarly, in the sites where *P. gingivalis* was detected but *T. forsythia* was not, the mean number of B cells was significantly larger than that of T cells
Beklen et al. (2008)	To study the expression and distribution of TLRs (1–10) in gingival tissue	Biopsies from 10 subjects with chronic periodontitis	IHC	In patients with periodontitis, epithelial cells showed increased TLR expression towards the basal layer. In the connective tissue, consistently higher TLR expression was found within the periodontitis group compared with the healthy group and most TLRs were detected in cells that morphologically resembled macrophages
Donati et al. (2008)	To study the local expression of IL-10 and CD14 in relation to − 1087 *IL-10* and − 159 *CD14* gene polymorphisms	Biopsies from 53 subjects with severe generalized chronic periodontitis	IHC	The proportion of the IL-10+ cells in the peripheral area of the periodontitis lesion was significantly larger in subjects with − 1087 IL-10 GG genotype than in subjects with AG or AA genotype. The local expression of the mCD14 did not vary between the subjects with different − 159 CD14 genotypes
Nakajima et al. (2008)	To evaluate CXCL13 Expression and follicular dendritic cell distribution in relation to B-cell infiltration in chronic inflammatory periodontal lesions	Gingival biopsies obtained from 58 subjects with moderate-to-advance chronic periodontitis	IHC	The number of CXCL13+ cells was significantly higher in periodontitis than in gingivitis in connective tissues subjacent to the pocket epithelium and positively correlated with the number of $CD19^+$ cells. CXCL13+ cells were distributed in B-cell-dominant areas both with and without follicular dendritic cells
Cardoso et al. (2009)	To study the presence of lymphocytes T helper type 17 in periodontitis lesion	Gingival and alveolar bone samples from 20 chronic periodontitis	IHC	Elevated levels Th17 cells in gingivae from patients with periodontitis were found. Moreover, IL-17 and the bone resorption factor RANKL were abundantly expressed in the alveolar bone of diseased patients, in contrast to low detection in controls
Donati et al. (2009)	To study the correlation between inflammatory cells and some functional markers in gingival lesions	Biopsies from 38 subjects with severe chronic periodontitis	IHC	B cells (B-1a and B-2 cells) occurred in larger proportions than T cells and plasma cells. A statistically significant correlation was found between the percentage of B-1a cells and plasma cells and between all B lymphocytes and plasma cells. About 60% of B lymphocytes exhibited autoreactive features
Koutouzis et al. (2009)	To compare and characterize the autoreactivity of LAgP and CP, to periodontally healthy controls	Biopsies from five chronic periodontitis, five local aggressive periodontitis	IHC Western blot ELISA	B cells autoreactivity to components of the periodontium was observed in CP and LAgP. Collagen and heat shock protein were identified along with multiple potential autoimmune targets. The autoreactivity to collagen type I observed in LAgP was more severe and diverse than that observed in CP
Kim et al. (2010)	To study host response in gingival tissue from periodontitis subjects and controls	Biopsies from eight chronic periodontitis subjects	ISH IHC	Compared with healthy sites, periodontal lesions contained a significantly increased number of each immune cell studied with a relative dominance of plasma cells over T cells
Lucas et al (2010)	To study whether the prolonged survival of inflammatory cells in periodontal disease could be due to the inhibition of apoptosis	Biopsies from 12 chronic periodontitis subjects	IHC	Higher levels of TRAIL were expressed in the diseased periodontal tissues. Statistically higher levels of cleaved caspase-3 and the cleaved caspase-3 inhibitors, xIAP and survivin, were seen. The results indicate that apoptosis in periodontitis may be inhibited by elevated expression of TRAIL decoy receptors and cleaved caspase-3 inhibitors
Oyarzun et al. (2010)	To study the type-I matrix metalloproteinase (MTI-MMP) in human periodontitis	Gingival biopsies 12 periodontitis subjects	IHC	Immunohistochemistry demonstrated expression of MT1-MMP in fibroblasts and macrophages in gingival tissues

IHC, immunohistochemistry; ISH, in situ hybridization.

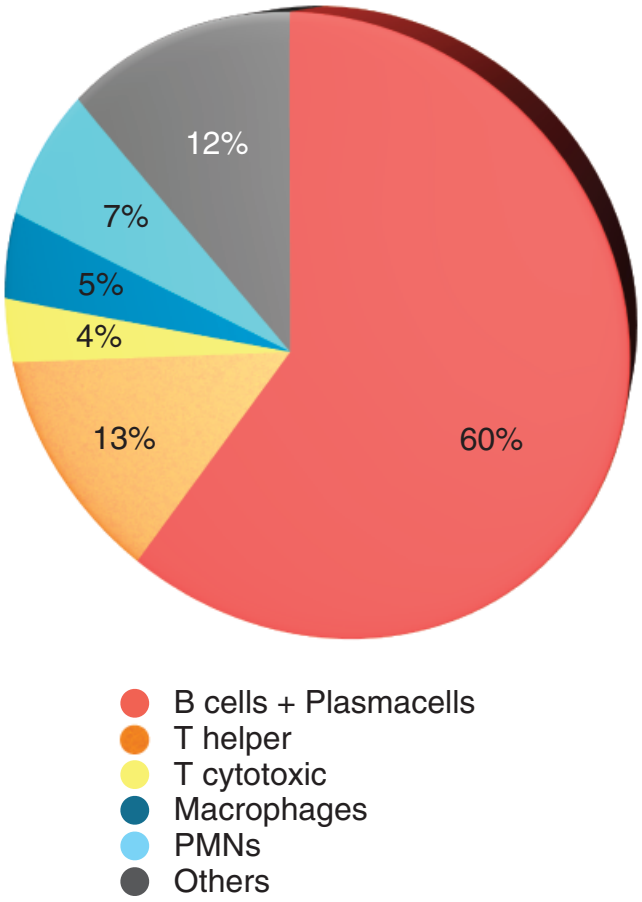

Fig. 1. Distribution of cell proportions in periodontitis lesions calculated from data in studies reported in Tables 2a and 2b.

cell proportions in periodontitis lesions is presented in Fig. 1. B cells and their subset plasma cells represented about 60% of cells in the lesion, while T helper and T cytotoxic cells presented with fractions of 13% and 4%, respectively. The proportions of PMN cells and macrophages in periodontitis lesions were about 7% and 5%, respectively.

In addition to the description of phenotype characteristics of cells in periodontitis lesions, recent studies included assessments of functional aspects also. Although comparisons between periodontitis lesions and healthy gingival tissues may be questioned, a general finding was that the expression of inflammatory markers and receptors is enhanced in periodontitis. Thus, in Table 2b several studies applied different techniques in tissue analysis and reported on elevated levels and proportions of, e.g., nuclear factor-kappa B (NF-κB) (Ambili et al. 2005), IL-2 receptor-positive T helper cells ($CD4^+$/$CD25^+$) (Nakajima et al. 2005), toll-like receptors (TLR) 2, 4, 7, and 9 (Ren et al. 2005, Beklen et al. 2008), matrix metalloproteinase (MMP) 1, 2, 3, 9, and 13 (Bodineau et al. 2006, Oyarzun et al. 2010) and receptor activator NF-κB ligand (Cardoso et al. 2009) in periodontitis lesions.

Experimental studies

While both periodontitis and peri-implantitis are infectious diseases, the important characteristics of the two conditions are the ensuing inflammatory reactions and associated tissue destruction that occur as a response to the biofilm residing on the tooth or implant surface. It was early understood that the infection and the resulting inflammation in gingival tissues required considerable time to elicit attachment and bone loss in periodontitis. Experiments in dogs demonstrated that natural development of periodontitis occurred after several years (Lindhe et al. 1973, 1975, Hamp & Lindberg 1977). Experimental models were therefore developed aiming at accomplishing rapid tissue destruction including loss of periodontal attachment and bone. Placement of ligatures made of cotton, silk, or other material around the neck of a tooth in a subgingival position together with undisturbed plaque formation is one of the most commonly used techniques to establish experimental breakdown of periodontal tissues. While the first attempts of ligature-induced breakdown of periodontal tissues were made in rats (Rovin et al. 1966), it has to be understood that rodents in general lack a natural propensity for periodontitis. Ligature models used in dogs and monkeys, however, were considered to produce periodontitis lesions, which in most respects mimicked natural lesions in humans. It is important to realize that the ligature-induced breakdown is a technical part of an experimental procedure to achieve a certain degree of breakdown and the final result of which will mimic a natural periodontitis lesion. It is thus not an ideal model to study progression, because the ligature-induced breakdown process can be controlled by the investigator. The type of ligature, the coronal–apical position of the ligature, and how often the ligature is replaced during the plaque formation period determine the rate and the amount of breakdown.

Early experimental periodontitis models in dogs and monkeys included the use of cotton or silk ligatures and the frequency of ligature replacement varied between studies (e.g. Kennedy & Polson 1973, Lindhe & Svanberg 1974, Ericsson et al. 1975, Schroeder & Lindhe 1975, 1980, Lindhe & Ericsson 1978). The placement of the ligature promoted initially a local minor trauma and, most important, an opening of the gingival pocket, which allowed biofilm formation to a profound subgingival position. This resulted in acute inflammatory reactions that involved early tissue breakdown and bone loss (Heijl et al. 1976). The breakdown process faded over time and the ligatures were therefore removed and replaced with a new set of ligatures in a more apical position to allow the processes to resume. The ligatures were finally removed when the desired amount of attachment and bone loss was accomplished.

Experimental peri-implantitis models have included the use of ligatures

around implants placed in dogs, monkeys, and mini-pigs. The current review included studies on experimental peri-implantitis that provided histopathological data on peri-implantitis lesions. Analysis of lesions produced from experimental periodontitis was made in studies evaluating both experimental conditions (Table 3). Lindhe et al. (1992) applied the ligature breakdown model around teeth and implants in five beagle dogs. Block biopsies from tooth and implant sites were obtained 1 month after the removal of ligatures. It was reported that clinical and radiographic signs of tissue destruction were more pronounced and that the size of the ICT in the connective tissue was larger around implants than teeth. The authors also pointed out that peri-implantitis lesions, in contrast to periodontitis lesions, reached the bone crest. It was suggested that the ''self-limiting'' process that occurred in the periodontal tissues after ligature removal did not take place in the peri-implant tissues. Schou et al. (1993) also evaluated experimental peri-implantitis in relation to experimental periodontitis. They applied ligatures around implants and normal and ankylosed teeth in cynomolgus monkeys. In accordance with the observations made by Lindhe et al. (1992), it was reported that bone loss was more pronounced around implants than around normal teeth. Schou et al. (1993) also reported that bone loss was associated with the histological finding of numerous osteoclasts. The lack of the ''self-limiting'' process following ligature removal in peri-implantitis observed by Lindhe et al. (1992) was examined in an animal experiment by Marinello et al. (1995). Ligature-induced breakdown was performed around 20 implants in five Labrador dogs. Block biopsies were obtained at 1 and 3 months after ligature removal in two and three dogs, respectively. The specimens representing 1 month demonstrated large ICTs that extended to the bone crest. Howships lacunae with osteoclasts were frequently found on the bone crest. In two of the three animals, from which biopsies were obtained 3 months after ligature removal, the peri-implantitis lesions were separated from the bone crest by a dense connective tissue capsule, while in the third animal in this group, three of the four implants were lost due to continuous breakdown after ligature removal. The remaining implant in this animal demonstrated extensive bone loss and the peri-implantitis lesion extended into the marrow spaces of the peri-implant bone. Osteoclasts were found on the surface of the bone crest.

Warrer et al. (1995) studied the influence of the type of mucosa around implants on experimental peri-implantitis in monkeys. It was reported that recession was more pronounced around implants with non-keratinized mucosa, while differences regarding remaining bone support were small between sites with keratinized and non-keratinized mucosa.

Studies were also performed to evaluate the effect of experimental peri-implantitis in combination with occlusal or lateral load on peri-implant tissues. Hürzeler et al. (1998) in an experiment in five cynomolgus monkeys found small differences in bone loss between peri-implantitis sites with and without occlusal load (2.6 versus 2.3 mm). The histological analysis revealed that the ICT in both types of peri-implantitis sites extended to the bone and that the pocket epithelium had migrated close to the bone crest. Gotfredsen et al. (2002) in an experimental study in dogs reported that lateral static load failed to enhance bone loss during experimental peri-implantitis. The extension of the large ICT in the peri-implant tissues was consistently apical of the pocket epithelium in both types of specimens.

As clinical diagnosis of peri-implantitis and periodontitis requires the use of a periodontal probe, experimental studies were performed to demonstrate the histological outcome following probing implant sites with peri-implantitis. Lang et al. (1994) in study in beagle dogs reported that probe penetration increased with the degree of inflammation in the tissues. Similar findings were made in an experimental study by Schou et al. (2002). They performed experimental breakdown with ligatures around teeth and implants in monkeys and observed that the probe tip was positioned further apical in sites with periodontitis and peri-implantitis than in sites with mucositis/gingivitis, and that the pocket epithelium exhibited apical migration in combination with extensive ulcerations in sites with experimental peri-implantitis. Schou et al. (2002) also identified osteoclasts in Howship's lacunae in sections from both experimental peri-implantitis and periodontitis.

A new model demonstrating spontaneous progression of experimental peri-implantitis was presented by Zitzmann et al. (2004). Initially, they performed ligature-induced breakdown around 22 implants in five Labrador dogs. When about 40% of the initial bone support was lost, the ligatures were removed. All sites were left with undisturbed continuing plaque formation during 12 months. While few implants demonstrated unchanged bone levels during the 12-month observation period, the majority of implants exhibited further progression of the disease with additional bone loss. Two implants were lost due to the continuous spontaneous breakdown of supporting tissues. The histological examination of the remaining eight peri-implantitis sites in three of the animals revealed that large inflammatory lesions extended apical of the pocket epithelium. The ICT in these sites was separated from the bone crest by a small zone of non-infiltrated connective tissue. Calculus, plaque, and pus resided in the pocket compartment. The spontaneous progression model of experimental peri-implantitis was subsequently used by Berglundh et al. (2007). They evaluated the influence of implant surface characteristics on spontaneous progression of the disease. While implants with a rough surface, in contrast to implants with a smooth surface, exhibited further bone loss during a 5-month period with plaque formation after ligature removal, the histological examination demonstrated advanced peri-implantitis lesions in both types of specimens. The pocket epithelium was ulcerated and the pocket area contained plaque, calculus, and pus. The large ICT extended apical of the pocket epithelium and, hence, the apical portion of the lesions was facing the contaminated implant surface. The morphological assessment of cell types in the lesion revealed hat plasma cells and lymphocytes dominated and that PMN cells occurred in high numbers. While the study by Berglundh et al. (2007) included implants with custom-made surfaces, Albouy et al. (2008, 2009) evaluated differences in spontaneous progression of experimental peri-implantitis between commercially available implants. Although the amount of spontaneous progression during a 6-month period after ligature removal differed among the implant types, all sites exhibited large inflammatory lesions that extended apical of

Table 3. Experimental studies on peri-implantitis and periodontitis

References	Number of animals/ implants/teeth involved	Experimental peri-implantitis/ implant system	Methods	Results
Lindhe et al. (1992)	Five dogs 10 implants 10 teeth	6 months plaque control after abutment connection Ligatures for 6 weeks at implants and contra-lateral pre-molars (replaced after 3 weeks) Plaque accumulation for additional 4 weeks Brånemark system	Clinical and radiographic examination of implants and teeth 1 month after ligature removal Biopsies from implant and tooth sites Histometric and morphometric measurements	Clinical and radiographic signs of tissue destruction more pronounced in PiM Ulcerated pocket epithelium in PiM and tooth sites ICT size greater in PiM than at tooth sites ICT: dominated by PMN and plasma cells in PiM, by macrophages and lymphocytes in tooth sites Alveolar bone: ICT extended into bone marrow of the alveolar bone at implant sites; non-inflammatory supraalveolar CT between ICT and alveolar bone crest at tooth sites
Schou et al. (1993)	Eight cynomolgus monkeys 16 implants 16 teeth (eight ankylosed maxillary molars and eight normal maxillary pre-molars)	3 months healing after implant placement Ligatures for 7 weeks at implants and teeth Titanium-coated cylindric polycarbonate implants	Block biopsies from implant and tooth sites Histologic analysis	Oral epithelium: totally parakeratinized at PiM, in part at tooth sites; intra- and inter-cellular oedema more pronounced at PiM than at tooth sites Pocket epithelium: thinner at implant than at tooth sites (most frequently 5–10 cell layer thick with extensive, irregular rete ridges), frequently ulcerated at PiM, while ulcerations at tooth sites were rare and limited to the ligature level PE terminated at or at varying distances above alveolar bone in PiMs, but no or minimal migration of PE at tooth sites ICT size: larger at PiM than at tooth sites Higher density of lymphocytes at PiM than at tooth sites More pronounced inflammatory changes at PiM (severe infiltrate with necrotic areas, increased vascularity, oedema, extravascular erythrocytes, loss of collagen) Alveolar bone: many osteoclasts and howships lacunae in PiM and ankylosed teeth (not at normal teeth), vertical defects around half of the implants (not at teeth)
Warrer et al. (1995)	Four monkeys 22 implants	3 month with plaque control Ligatures for 9 months at eight implants in keratinized mucosa (KM) and eight implants in lining mucosa, six implants with plaque only for 9 months (without ligatures) ITI hollow-cylinder with TPS surface	Clinical examination (PI, GI, PPD, PAL) at 3-month intervals Biopsies from implant and tooth sites Histometric analysis	PiM without KM demonstrated significantly more recession, more attachment loss and increase in probing depth than sites with KM ICT: limited to supracrestal region (soft tissue between apical termination of the epithelium and alveolar bone) Bone loss: present in sites with plaque only, increased by ligatures, more severe when KM is lacking Remaining bone height (osseointegrated part of the implant in percentage of total length): 65% with KM and plaque only, 63% with KM and ligatures, 62% no KM and plaque only, 54% no KM and ligatures

Table 3. (Contd.)

References	Number of animals/ implants/teeth involved	Experimental peri-implantitis/ implant system	Methods	Results
Marinello et al. (1995)	Five dogs 20 implants	Abutment connection 3 months after implant placement After 6 months ligatures for 4–6 weeks (tissue destruction amounted 25% of the original bone height) Plaque accumulation for additional 1–3 months –Two dogs sacrificed after 1 month, three dogs sacrificed 3 months after ligature removal Brånemark	Clinical examinations before block biopsy at 1- and 3-month intervals after ligature removal Histometric and morphometric analyses	After 1 month: Ulcerated pocket epithelium ICT extended from mucosal margin to bone crest ICT composition: 29% collagen, 19.9% vascular structures, 8% fibroblasts, 16.5% inflammatory cells (9% plasma cells, 3% T cells, 2% macrophages, 2% PMNs) Apical ICT portion in direct contact with implant surface and bone (Howship's lacunae with osteoclasts) After 3 months: Pocket epithelium ICT resting and encapsulated by dense collar of fibrous CT separating from bone ICT composition: 36.5% collagen, 11.2% vascular structures, 4.6% fibroblasts, 28.5% inflammatory cells (20% plasma cells, 1% T cells, 2% macrophages, 5% PMNs) No signs of inflammation within the marrow spaces of the bone (two of three dogs)
Hürzeler et al. (1998)	Five cynomolgus monkeys 20 implants	Abutment connection 4 months after implant installation After 4 weeks restoration with single crowns Ligatures for 4 months (replaced once every 4 weeks) Mechanical trauma with orthodontic devices on two of four implants for additional 4 months (excessive occlusal load during mouth opening) Sacrifice after 4 months Brånemark	Block biopsies and ground sections Histologic analysis	Subgingival plaque deposits Pocket epithelium migrated down to the alveolar crest ICT extended to the bone (no CT between apical extension of epithelium and bone) Lower two-thirds of the implant was osseointegrated in compact alveolar bone, upper third of the implant was adjacent to the ICT Similar amount of bone loss irrespective of trauma (with trauma 2.6 mm, without trauma 2.3 mm)
Gotfredsen et al. (2002)	Five dogs 20 implants	3 months with plaque control Connection of appliance with expansion screw at central and posterior implants Ligatures at anterior and posterior implants for 4 months 2 months after ligature removal: activation of expansion screws for 3 months Sacrifice at week 60 Experimental turned and SLA surfaces (ITI)	Radiographs every 2 weeks between weeks 24 and 60 Block biopsies Histology	ICT exceeded apical termination of the epithelium Similar amount of bone loss irrespective of load (with load 6.3 mm, without load 6.5 mm)
Schou et al. (2002)	Four cynomolgus monkeys Eight implants Eight teeth (second pre-molars or second molars)	3 months healing after implant placement Ligatures secured by orthodontic elastics for 7 months at implants and for 4 months at teeth (replaced or pushed apically once every 4 weeks) Experimental implants with machined surface (Astra)	Block biopsies from implant and tooth sites Histologic analysis	Pocket epithelium: apical migration at implant and tooth sites, extensive ulceration only at implant sites 2-4 mm bone loss, Howship's lacunae and osteoclasts at implant and tooth sites
Zitzmann et al. (2004)	Five dogs 22 implants	Abutment connection 4 months after implant placement After additional 5 months ligature placement for 2 months	Radiographs at ligature placement, at ligature removal and at final examination at 14 months (all five dogs and 22	Calculus on the implant surface Ulcerated pocket epithelium separated ICT from plaque and pus in the pocket

Table 3. (Contd.)

References	Number of animals/ implants/teeth involved	Experimental peri-implantitis/ implant system	Methods	Results
		Plaque accumulation for additional 12 months Brånemark	implants) Block biopsies Histology (three dogs and eight implants)	ICT: extended apically of PE, separated from bone by non-inflamed CT ICT composition: dominated by plasma cells, lymphocytes, PMNs, macrophages, vascular structures, few collagen and fibroblasts Marginal bone: frequently secondary osteons and reversal lines, only few osteoclasts
Berglundh et al. (2007)	Five dogs 30 implants	3 months with plaque control Ligatures for 4 months (replaced once every 2 weeks), 40% of supporting bone lost Plaque accumulation for additional 5 months 15 implants with sandblasted acid-etched surface (SLA), 15 implants with polished surface Solid screw implants (Straumann)	Block biopsies Radiographic measurements Histologic analysis	Implant surfaces: soft and mineralized microbial deposits, with layer of PMN cells and necrotic tissue Ulcerated pocket epithelium: separates marginal portion of PiM from the pocket area Apical no epithelial barrier between ICT and implant Large ICT: dominated by plasma cells, PMN cells Upper marginal portion of ICT: mainly lymphocytes ICT apical of pocket epithelium and adjacent to implant surface: larger numbers of PMNs and vascular structures, no collagen and fibroblasts Marginal bone: at central or apical third of the intra-osseous part of the implant
Albouy et al. (2009)	Six dogs 64 implants	3 months with plaque control Ligatures for 3 months (replaced once every 3 weeks), 40–50% supporting bone lost Plaque accumulation for additional 6 months Turned surface (Biomet3i), TiOblast Astra Tech, SLA (Straumann), TiUnite (Nobel Biocare)	Block biopsies Histology	Ulcerated pocket epithelium (along 40–60% of the vertical dimension of the pocket) Apical part of the pocket: no epithelial barrier between ICT and pus or microbial deposits on the implant surface ICT lateral to PE or pus: PMNs dominating ICT centre: lymphocyts and plasma cells dominating, multi-nucleated giant cells in the area in contact with biofilm or pus; dense vascular units with emigrating leukocytes Apical ICT close to the bone: numerous osteoclasts with Howship's lacunae, multi-nucleated cells also lateral to the osseous surface Crater-like osseous defects

PI, peri-implantitis; PiM, peri-implant mucosa; ICT, inflammatory cell infiltrate in the connective tissue; CT, connective tissue; PE, pocket epithelium; PPD, probing pocket depth; PAL, porbing attachment level; BoP, bleeding-on-probing; PMN, polymorphonuclear cells.

an ulcerated pocket epithelium. Pus, plaque, and calculus were found in the pocket areas and the uncovered apical zone of the ICT was facing the biofilm that resided on the implant surface. The ICT, which extended close to the bone crest, contained large numbers of lymphocytes and plasma cells. PMN cells were found in high numbers in areas close to the pocket and in peri-vascular compartments in profound regions of the lesion. All specimens demonstrated osteoclasts lining the surface of the bone. Multi-nucleated cells were also found in ICT areas distant from the bone.

Discussion

In the present review, the question whether peri-implantitis lesions are different from periodontitis lesions was addressed. Data collected from studies on human biopsy material and from animal experiments were analysed.

While comprehensive information exists regarding histopathological characteristics of human periodontitis lesions, few studies have evaluated peri-implantitis lesions in human biopsy material. Studies aiming to apply structured comparisons between the two types of lesions in human material are virtually lacking. The analysis carried out in the review regarding experimental peri-implantitis revealed that few studies were performed to examine the histopathological characteristics of the lesions and only three studies included comparisons with experimental periodontitis.

There are obvious advantages of using human biopsy material in the analysis of peri-implantitis and periodontitis lesions. The specimens from humans provide direct information from diseased sites and the availability to apply numerous techniques for analysis of cell functions and structures. The disadvantages with human biopsies relate to variations in severity of the disease and the limited accessibility to obtain representative parts of the lesion during the biopsy procedure. The retrieval of soft-tissue biopsies may often fail to include the entire inflammatory lesions at sites with peri-implantitis and periodontitis. Human biopsies will normally not include bone tissue.

There are also advantages when using experimental models in peri-implantitis and periodontitis. Not only the severity of the disease can be controlled, block biopsies provide unrestricted access to the entire lesion including surrounding hard tissue. In other words, the model allows analysis of the diseased site in situ. Furthermore, different test systems of influencing factors, such as implant surface and geometry can also be applied. With regards to disadvantages, the relevance of the experimental model has to be verified. It is generally agreed that the lesions produced from experimental periodontitis using ligatures resemble natural occurring periodontitis lesions as assessed from human biopsies and autopsy material. In peri-implantitis, however, comparisons between similar experimental models and human autopsy material are presently not possible. Comparisons between the results obtained from experimental peri-implantitis and the data obtained from analysis of human biopsy material from sites with peri-implantitis must be carried out with consideration to the limitations.

Conclusions

Human biopsy material

1. Specimens obtained from sites with peri-implantitis and periodontitis lesions exhibited large ICTs lateral to a pocket epithelium.
2. The apical extension of the ICT was more pronounced in peri-implantitis than in periodontitis and was in most cases of peri-implantitis located apical of the pocket epithelium.
3. Plasma cells and lymphocytes dominated among cells in both types of lesions, whereas neutrophil granulocytes and macrophages occurred in larger relative proportions in peri-implantitis than in periodontitis.
4. While neutrophil granulocytes in periodontitis lesions reside in pocket-epithelium-associated areas, the location in peri-implantitis lesions also included perivascular compartments in apical portions distant from the pocket area.
5. In contrast to the description of periodontitis lesions, analysis of human biopsy material of peri-implantitis lesions frequently revealed that the apical portion of the ICT was uncovered and was facing the pocket area.

Experimental studies

1. Placement of ligatures in a submarginal position together with undisturbed plaque formation resulted in substantial loss of supporting tissues and the establishment of large ICTs around implants and teeth in animals.
2. The tissue reaction following ligature removal was different at implants and teeth. A ''self-limiting'' process occurred in the tissues around teeth that resulted in a protective connective tissue capsule that separated the ICT from bone at 1 month after ligature removal. Such a ''self-limiting'' process did not take place in peri-implant tissues following ligature removal and the ICT extended to the bone crest.
3. Experimental peri-implantitis sites, in contrast to experimental periodontitis, exhibited signs of acute inflammation and large amounts of osteoclasts that lined the surface of the bone crest at varying periods after ligature removal.
4. The ICT in peri-implantitis sites consistently extended apical of the pocket epithelium. The uncovered apical portion of the ICT was in direct contact with the biofilm residing on the implant surface.
5. Analysis of the composition of the ICT revealed that plasma cells and lymphocytes dominated in both types of lesion. PMN cells and macrophages, however, occurred in larger numbers in peri-implantitis than in periodontitis.
6. Recent development of the experimental peri-implantitis models demonstrated that lesions produced from ligature-induced breakdown and plaque formation also progressed with additional bone loss after the removal of ligatures. Similar effects have not been demonstrated for experimental periodontitis.

Despite similarities regarding clinical features and aetiology of peri-implantitis and periodontitis, critical histopathological differences exist between the two lesions. Such differences are important to consider in the planning of treatment protocols for peri-implantitis.

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Address:
Tord Berglundh
Department of Periodontology
The Sahlgrenska Academy
University of Gothenburg
Box 450
SE 405 30 Göteborg
Sweden
E-mail: tord.berglundh@odontologi.gu.se

Clinical Relevance

Scientific rationale for the study: While peri-implantitis and periodontitis have many clinical features in common, structural differences in supporting tissues between implants and teeth may influence host response to infection. The review was conducted to answer the question whether peri-implantitis lesions are different from periodontitis lesions.

Principal findings: The apical extension of the ICT was more pronounced in peri-implantitis than in periodontitis and was in most cases located apical of the pocket epithelium. Plasma cells and lymphocytes dominated among cells in both types of lesions, whereas neutrophil granulocytes and macrophages occurred in larger proportions in peri-implantitis. Placement of ligatures together with plaque formation in animal experiments resulted in loss of supporting tissues and large ICTs around implants and teeth. Following ligature removal, a ''self-limiting'' process occurred in the tissues around teeth with a connective tissue capsule that separated the ICT from bone, while in peri-implant tissues, the ICT extended to the bone crest.

Practical implications: Despite similarities regarding clinical features and aetiology of peri-implantitis and periodontitis, critical histopathological differences exist between the two lesions. Such differences are important to consider in the planning of treatment protocols for peri-implantitis.