Experimentally Induced Peri-implantitis: A Review of Different Treatment Methods Described in the Literature

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The aim of this article was to present the experimental peri-implantitis models described in the literature and to provide a review of currently used treatment methods. For this purpose, 29 English- and German-language studies published in internationally reviewed journals were examined for similarities and differences regarding animal models, types of implants, and methods used for inducing peri-implantitis. In almost all studies, the implants were located in the mandible, which suggests that peri-implantitis of the maxilla has been researched very little. While in most studies, peri-implantitis was induced by means of ligature and plaque accumulation, only 3 studies have been published that attempted to induce peri-implantitis by means of mechanical overload. Of the latter, only one author observed peri-implant bone resorption. Eleven studies reporting on ligature-induced peri-implantitis presented enough data to be subjected to further statistical data analyses. Meta-analysis revealed that the period of ligature application, and thus the duration of plaque accumulation, generally had no influence on the resultant depth of the bone defect. However, when screw-type and cylindric implants were analyzed separately, a weakly significant positive effect of the duration of ligature application on the resultant defect depth was determined for cylindric implants (P = .092). This could imply that smooth screw-type implants were less susceptible to ligature-induced peri-implant inflammation. Regenerative treatment methods included the membrane technique using non-resorbable membranes (guided bone regeneration), augmentation with autogenous bone, augmentation with bone substitute materials (hydroxyapatite or demineralized freeze-dried bone) or with recombinant human bone morphogenetic protein-2, and a combination of membrane and augmentation procedures. While all described methods resulted in acceptable bone gain, it seems to be difficult to achieve new osseointegration (reosseointegration) of treated implants. Of all tested treatment methods, the combination of guided bone regeneration and augmentation with demineralized freeze-dried bone resulted in the most favorable results regarding bone gain and reosseointegration. (Int J Oral Maxillofac Implants 2000;15:533–544)

Key words: *peri-implantitis, review literature, treatment outcome*

Improved osseiointegration techniques have led to considerable improvement of the long-term prognosis of dental implants in the past few decades.[1,2] Nevertheless, implant failures do occur and can be classified on the basis of both chronologic (early and late) and etiologic aspects.[3,4] Late failures are commonly associated with the occurrence of peri-implantitis.

Peri-implantitis is diagnosed when progressive peri-implant bone loss occurs that exceeds the limits of tolerable bone resorption after the successful osseointegration of an implant.[5] Possible causes include bacterial genesis (plaque theory),[6,7] occlusal overload (loading theory),[8–11] or a combination of these factors.

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Peri-implantitis caused by microorganisms begins with inflammation of the peri-implant mucosa (mucositis), which is usually reversible.[12] However, if left untreated, the inflammation spreads apically and results in vertical and horizontal bone loss and eventually in the loss of the implant. For this reason, implants affected by peri-implantitis may demonstrate little clinical mobility until the final stage of peri-implantitis is reached. Among the microorganisms believed to cause peri-implantitis, *Prevotella intermedia*, *Porphyromonas gingivalis*, and *Fusobacterium sp.* are currently the subject of numerous microbiologic studies.[13,14] Many authors believe that the microorganisms that cause peri-implantitis and periodontitis are one and the same, at least in the partially dentate arch.[15] In contrast to plaque-induced peri-implantitis, peri-implantitis caused by occlusal overload starts with microfractures of the peri-implant bone and is reported to occur without any noticeable signs of inflammation in the initial phase.[16]

Although it is important that the etiology and diagnosis of peri-implantitis be the subject of scientific research, it is even more important to find an optimum treatment. Ideally, treatment of peri-implantitis aims to restore conditions favorable to osseointegration. To achieve this goal, the causes of peri-implantitis must be eliminated, and then the restoration of the original peri-implant condition must be attempted. Conservative, resective, and regenerative treatment measures have been described, depending on the type and size of the bone defect.[17,18] During the initial stage of peri-implantitis, attempts must be made to eliminate the inflammation by means of optimum oral hygiene carried out by the patient and simultaneous treatment with antimicrobial and anti-inflammatory substances (eg, chlorhexidine). Resective and regenerative treatment methods for advanced bone resorption, on the other hand, require surgical intervention. The aim of treatment is either to decontaminate the implant surface, remove granulation tissue, and level the bone defect (resective treatment), or to restore the lost bone following surface decontamination by means of different methods (regenerative treatment). Few experimental studies[10,11,19–26] have examined the value of different treatment measures, and clinical experiences were published mainly as case reports.[27–29] Only 2 clinical studies reviewed the treatment results of larger groups of patients.[30,31]

The aim of this review of literature was to examine the available animal experimental studies on peri-implantitis for generally valid guidelines and to demonstrate the current state of the art in regenerative treatment of peri-implantitis on the basis of these studies.

MATERIALS AND METHODS

Medical databases CCSearch 5Sci.Ed. (1997–1999), Medline Advanced (1996–1999), Toxline Plus (1994–1999), Embase CD (1989–1999), and Pascal-Biomed (1996–1999) were searched for the term "peri?implantitis" by means of WinSPIRS and the respective references were analyzed. The summary of the model for peri-implantitis was based exclusively on English-language and German-language studies published in internationally reviewed journals.

For further statistical analysis of possible influencing factors of the animal model on peri-implantitis, the only studies that were used were those in which experimental peri-implantitis had been induced by means of ligature, the resultant bone defect had been measured intraoperatively or histomorphometrically, and the results had been reported from random sampling (scope of the sample, mean value, and standard deviation). To avoid overrating possible influencing factors in the statistical results, study data with the same implant design and the same duration of ligature application were united in a single random sample result. A correlation analysis was then carried out for the period of application of the peri-implantitis–inducing ligature and the resultant bone resorption by means of Pearson's correlation coefficient. Coated cylindric implants and uncoated screw-type implants were considered in the analysis, both together and separately. Adequate statistical analysis of data on peri-implantitis induced by excessive loading was not possible, as only 3 studies were available on this subject, and no other methods of induction of experimental peri-implantitis were evaluated. SAS software (SAS, Cary, NC) was used for statistical data evaluation. *P* values less than .05 were considered statistically significant.

RESULTS

The initial search revealed 96 studies. A total of 87 studies met the required criteria. Of these studies, 14 were reviews, 9 were in vitro studies, 23 were clinical studies, 12 were case reports, and 29 were experimental studies of peri-implantitis. The animal models applied in the 29 experimental studies were examined. Of these, 11 studies exclusively examined the objectifiable results of peri-implantitis induction, 6 analyzed the value of different diagnostic methods, and 13 researched the value of conservative or regenerative treatment measures (Table 1).

Further results of the statistical analysis regarding possible factors influencing peri-implantitis

Table 1 Experimental Studies of Peri-implantitis Listed According to Animal Species Examined, Number of Experimental Animals and Pre-implantation Measures

			Pre-implantation measures	
Study	Species	No. of animals	Extracted teeth	Healing period (mo)
Brägger et al (1991)[36]	Dog	1	Unknown	Unknown
Günay et al (1991)[19]	Monkey	6	1	0
Hickey et al (1991)[7]	Pig	2	Unknown	4
Jovanovic et al (1992)[21]	Dog	3	5	3
Grunder et al (1993)[20]	Dog	10	2	6
Singh et al (1993)[22]	Pig	2	Unknown	Unknown
Lang et al (1994)[12]	Dog	5	3	4
Schüpbach et al (1994)[23]	Dog	5	2	6
Weber et al (1994)[38]	Dog	2	5	3
Cook and Rust-Dawicki (1995)[32]	Dog	14	4	2
Hürzeler et al (1995)[10]	Dog	7	5	3
Marinello et al (1995)[40]	Dog	5	3	3
Warrer et al (1995)[37]	Monkey	5	3	3
Ericsson et al (1996)[39]	Dog	5	3	3
Isidor (1996)[9]	Monkey	4	7	8
Persson et al (1996)[24]	Dog	5	3	3
Fritz et al (1997)[33]	Monkey	36	Unknown	6
Hanisch et al (1997a)[25]	Monkey	4	5	3
Hanisch et al (1997b)[41]	Monkey	4	3	3
Hürzeler et al (1997)[11]	Dog	7	5	3
Isidor (1997a)[16]	Monkey	4	7	8
Isidor (1997b)[35]	Monkey	4	7	8
Tillmanns et al (1997)[34]	Dog	14	3	3
Eke et al (1998)[13]	Monkey	6	1	Unknown
Hürzeler et al (1998)[42]	Monkey	5	4	3
Isidor (1998)[50]	Monkey	4	7	8
Miyata et al (1998)[43]	Monkey	5	2	3
Tillmanns et al (1998)[14]	Dog	14	3	3
Wetzel et al (1999)[26]	Dog	7	4	5

refer exclusively to those 11 studies that were usable because of the applied measuring methods and the data given. In these 11 studies, a total of 263 implants, with 164 cylindric and 99 screw-type, were evaluated. When the data were united in single-sample results, 15 sample groups (8 with cylindric and 7 with screw-type implants) remained (Table 2).

Model and Method of Induction

Experimental Animals. To examine peri-implantitis, either monkeys, dogs, or pigs were used, ie, highly developed experimental animals. Furthermore, all studies examined a single species in relatively small groups of up to 10 experimental animals. Only 4 studies evaluated a larger group of animals (Table 1).[14,32–34]

During the presurgical phase, 2 to 7 premolars and/or molars were extracted from the animals' mandibles. The extraction sites were then left to heal for 2 to 8 months before the implants were placed. In only 1 study were implants placed immediately after extraction (Table 1).[19]

In almost all studies, the mandibular posterior region was chosen as the location for the implants. Isidor placed 1 additional implant in the anterior mandible.[9,16,35] Only 1 study reported on the induction and treatment of experimentally induced peri-implantitis in the maxilla.[25] Thus, while mandibular experimental peri-implantitis has been investigated to some extent, practically no scientific data are available on peri-implantitis in the maxilla.

Implants. Each experimental animal underwent the placement of 2 to 5 implants in each side of each arch. All but 4 studies used 2-stage implant systems.[12,26,36,37] No study is currently available on possible differences in effect on experimental peri-implantitis between 1- and 2-stage implant systems. Implants used were mainly uncoated screw-type and coated cylindric implants (Table 3). The surfaces of

Table 2 Studies of Ligature-Induced Peri-implantitis That Were Available for Statistical Analyses

	Type of implant				Peri-implant defect	
Study	Shape	Coating	No. of implants	Plaque accumulation (wk)	Defect depth ± SD (mm)	Measuring method
Cook and Rust-Dawicki[32]	C	CSTi	8	4	1.43 ± 1.19	Histometric analysis
	C	HA	8	4	2.1 ± 1.37	
	C	CSTi	10	8	1.92 ± 1.13	
	C	HA	8	8	1.82 ± 1.4	
	C	CSTi	9	16	2.07 ± 0.92	
	C	HA	8	16	1.6 ± 0.57	
	C	CSTi	14	26	1.96 ± 0.94	
	C	HA	28	26	2.69 ± 1.27	
Persson et al[24]	S	U	15	6	1.8 ± 0.45	Histometric analysis
Isidor[16, 35]	S	U	12	78	2.37 ± 0.93	Histometric analysis
Warrer et al[37]	C	TPS	12	26	3.8 ± 0.77	Histometric analysis
Hürzeler et al[10, 11]	S	U	7	13	4.1 ± 0.5	Intraoperative
	S	U	7	13	3.5 ± 0.3	
	S	U	7	13	3.5 ± 0.6	
	S	U	7	13	3.3 ± 0.6	
	S	U	7	13	3.3 ± 0.6	
	S	U	7	13	3.2 ± 1.0	
Hanisch et al[25]	C	HA	15	47	3.4 ± 0.9	Intraoperative
	C	HA	16	47	3.2 ± 0.9	
Tillmanns et al[14]	C	HA	6	13	1.63 ± 1.24	Histometric analysis
	C	TPS	6	13	2.08 ± 1.15	
	S	U	6	13	2.19 ± 1.19	
	C	HA	8	26	1.84 ± 1.16	
	C	TPS	8	26	1.39 ± 1.0	
	S	U	8	26	1.75 ± 0.59	
Singh et al[22]	S	U	2	6	3.0 ± 0.92	Intraoperative
	S	U	2	6	2.94 ± 0.49	
	S	U	2	6	3.75 ± 0.46	
Hürzeler et al[42]	S	U	10	32	2.3 ± 0.6	Histometric analysis

CSTi = cancellous structured titanium; HA = hydroxyapatite; TPS = titanium plasma-flame-spray; U = uncoated; C = cylindric; S = screw-type; SD = standard deviation.

coated implants consisted either of hydroxyapatite (HA), titanium plasma-flame-spray (TPS), or a cancellous structured titanium (CSTi) porous coating (Table 3).

No significant differences were found in the development and the course of peri-implantitis around different types of coated implants after an observation period of up to 6 months.[14,32,34] Only Jovanovic et al[21] reported greater peri-implant bone resorption around HA-coated implants. Two[7,23,32] to 6[9,13,24] months after implant placement, the implants were uncovered in a secondary surgical procedure and abutments were connected.

Four authors administered antibiotics postoperatively.[7,12,32,37] This therapy consisted either of a single intramuscular administration of penicillin[7,37] or a 5-day antibiotic prophylaxis (penicillin).[12,32] Weber et al[38] carried out preoperative antibiotic therapy (600,000 IU Bicillin intramuscularly).[38] No differences in the osseointegration behavior or in failure rates were found.

In most cases, a plaque regimen usually consisting of mechanical cleaning by means of brushes and water,[24,39,40] toothpaste,[32] or an abrasive agent (fluorine pumice)[10,11,23,26] was carried out following uncovering of the implants. In some studies, the implants were also cleaned with scalers and polished afterwards.[13,14] Some authors also carried out chemical plaque control by means of chlorhexidine (concentrations of 0.12%, 0.2%, or 2%) in addition to mechanical cleaning (Table 4).[11,26,37,41]

Induction of Peri-implantitis. Peri-implantitis was induced either by excessive loading of the implants or by excessive plaque accumulation.

Overload-Induced Peri-implantitis. To date, few studies have investigated mechanically induced peri-implantitis.[9,42,43] In these studies, mechanical overload was achieved by providing premature contact at the occlusal plane, which either bumped into a metal splint attached to the maxilla[9,42] or into natural dentition,[43] thus inducing repetitive mechanical trauma. In addition to the axial trauma, buccal[9,43] or

Table 3 Information on Implant Shapes and Coatings Used in Studies on Experimentally Induced Peri-implantitis

Study	No. of implants	Implant shape	Surface
Brägger et al (1991)[36]	2	Cylindric	Uncoated
Günay et al (1991)[19]	12	Screw	Uncoated
Hickey et al (1991)[7]	12	Screw	Uncoated
Jovanovic et al (1992)[21]	30	Cylindric, screw	Uncoated and HA, TPS
Grunder et al (1993)[20]	40	Screw	Uncoated
Singh et al (1993)[22]	12	Screw	Uncoated
Lang et al (1994)[12]	30	Cylindric	TPS
Schüpbach et al (1994)[23]	20	Screw	Uncoated
Weber et al (1994)[38]	20	Cylindric	Uncoated
Cook and Rust-Dawicki (1995)[32]	84	Cylindric	CSTi, HA
Hürzeler et al (1995)[10]	42	Screw	Uncoated
Marinello et al (1995)[40]	20	Screw	Uncoated
Warrer et al (1995)[37]	22	Cylindric	TPS
Ericsson et al (1996)[39]	30	Screw	Uncoated
Isidor (1996)[9]	20	Screw	Uncoated
Persson et al (1996)[24]	30	Screw	Uncoated
Fritz et al (1997)[33]	43	Screw, plate form	Uncoated
Hanisch et al (1997a)[25]	32	Cylindric	HA
Hanisch et al (1997b)[41]	32	Cylindric	HA
Hürzeler et al (1997)[11]	42	Screw	Uncoated
Isidor (1997a)[16]	20	Screw	Uncoated
Isidor (1997b)[35]	20	Screw	Uncoated
Tillmanns et al (1997)[34]	84	Cylindric, screw	Uncoated and HA, TPS
Eke et al (1998)[13]	7	Screw, plate form	Uncoated
Hürzeler et al (1998)[42]	40	Screw	Uncoated
Isidor (1998)[50]	20	Screw	Uncoated
Miyata et al (1998)[43]	10	Cylindric	TPS
Tillmanns et al (1998)[14]	84	Cylindric, screw	Uncoated and HA, TPS
Wetzel et al (1999)[26]	41	Cylindric	Uncoated and TPS

mesiodistally[42] directed overloading was achieved by means of suprastructure design. This device was attached to the arch for 1 to 4 weeks,[43] 16 weeks,[42] or 18 months.[9] To eliminate the microbial component of peri-implantitis, the implants were simultaneously subjected to a plaque regime. The studies yielded completely contrary results. While Hürzeler et al[42] and Miyata et all[43] found no significant loss of osseointegration in occlusally overloaded implants, Isidor[9] observed clinical mobility in 6 of 8 implants, 2 of which were lost.

A remarkable finding was the great variation in the duration of mechanical overload, which might explain the differing results. Isidor[9] observed implant mobility caused by progressive resorption after exposing the implants to mechanical trauma for 18 months. After 4.5 months, one implant was lost. Other implants demonstrated clinical mobility after 5.5, 15, and 15.5 months, respectively, ie, at a time when other authors had already concluded their experiments. Another reason for the contrasting results might be the achievement of a certain threshold value that was described only as "excessive," but was not indicated as a quantifiable value. It can thus be assumed that occlusal overload likely causes implant failure if the load exceeds a certain threshold value and/or acts on the implant for a sufficiently long period of time (Table 5).

Ligature-Induced Peri-implantitis. In all other studies, peri-implant inflammation was induced by means of a ligature placed around the cervical end of the implant, which caused increased plaque accumulation. After up to 2 months, peri-implantitis was objectively demonstrated around all implants. In evaluating the 11 statistically analyzable studies (Table 2), it was found that the ligature method resulted in a bone defect 1.4 to 4.1 mm deep and a mean bone loss of 2.38 mm (SD 0.72 mm). The type of implant used had no effect on bone resorption, which was roughly the same around cylindric implants (2.31 ± 0.81 mm) and screw-type implants (2.45 ± 0.67 mm) (P = .52). This finding is consistent with findings of Tillmanns

Table 4 Pre- and Postoperative Care of Implant Sites in Studies of Experimental Peri-implantitis

Study	Antibiotic	Implant healing (mo)	Plaque regimen		
			Timing	Duration (mo)	Method
Brägger et al (1991)[36]			—	—	—
Günay et al (1991)[19]		3	—	—	—
Hickey et al (1991)[7]	1× penicillin IM postop	2	—	—	—
Jovanovic et al (1992)[21]			—	—	—
Grunder et al (1993)[20]		2	Before PI	2	Brush, pumice
Singh et al (1993)[22]			—	—	—
Lang et al (1994)[12]	Penicillin for 5 days postop		Before PI	2	Pumice, chlorhexidine
Schüpbach et al (1994)[23]		2	Before PI	3	Brush, pumice
Weber et al (1994)[38]	600,000 IU bicillin preop	3	Before PI	3	Chlorhexidine gel
Cook and Rust-Dawicki (1995)[32]	Antibiotic IM for 5 days postop	2	—	—	—
Hürzeler et al (1995)[10]		3	After PI	1	Chlorhexidine, pumice
Marinello et al (1995)[40]		3	Before PI	6	Brush
Warrer et al (1995)[37]	1× penicillin IM postop		Before PI	3	Chlorhexidine
Ericsson et al (1996)[39]		3	Before PI	3	Brush
Isidor (1996)[9]		6	—	—	—
Persson et al (1996)[24]		6	Before PI	3	Brush
Fritz et al (1997)[33]		3	—	—	—
Hanisch et al (1997a)[25]			Before PI	3	Chlorhexidine
Hanisch et al (1997b)[41]		12	Before PI	3	Chlorhexidine
Hürzeler et al (1997)[11]		3	After PI	1	Chlorhexidine, pumice
Isidor (1997a)[16]		6	—	—	—
Isidor (1997b)[35]		6	—	—	—
Tillmanns et al (1997)[34]		3	Before PI	—	Brush, scaling
Eke et al (1998)[13]		6	Before PI	—	Brush, scaling
Hürzeler et al (1998)[42]		4	Before PI	0.75	Chlorhexidine, pumice
Isidor (1998)[50]		6	—	—	—
Miyata et al (1998)[43]		3	—	—	—
Tillmanns et al (1998)[14]		3	Before PI	—	Brush, scaling
Wetzel et al (1999)[26]	Penicillin for 5 days postop	0	Before PI	3	Pumice, chlorhexidine

IM = intramuscularly; Before PI = prior to induction of experimental peri-implantitis; After PI = following induction of experimental implantitis; — = no plaque regimen.

et al[14] and Wetzel et al,[26] who observed peri-implant bone defects of comparable depth around coated and uncoated implants (Table 2).

In only 2 studies was a defect that was an additional 2 to 3 mm deep created surgically in which ligatures were placed, emerging from the mucosa via the surgical wound.[19,21] All studies in which a ligature was placed around the cervical of the implant to provoke plaque accumulation were successful in inducing peri-implantitis.

The time during which ligatures were left in place varied between 1 month[32,40] and 18 months,[9] the mean application period being 22.7 weeks (SD 19.3 weeks). The period of ligature application had no effect on the severity of bone resorption in all examined studies (r = 0.169; P = .548). However, when both types of implants were evaluated separately, no significant effect of the period of ligature application on bone resorption was found for screwtype implants (r = –0.038; P = .935), whereas a borderline significant positive effect was observed for cylindric implants (r = 0.633; P = .092). This means that, in larger test groups, cylindric implants might demonstrate deeper bone defects over a longer period of ligature application.

In a weighted analysis of covariance with random effects (study nested in implant design) regarding implant design, period of ligature application, and the interaction between implant design and period of ligature application, the unknown study effect had a significant influence on the amount of bone resorption observed (P = .014). Thus a non-discernible factor in the study model must have a decisive influence on the severity of peri-implantitis. Regrettably, it was not possible to further analyze possible influencing factors because of the limited number of studies, differences in study models used, and incomplete data provided. However, because of the relatively small number of implants available for statistical analysis, conclusions are valid to a limited degree.

Table 5 Comparison of Microbially and Mechanically Induced Peri-implantitis

	Ligature			Overload		
Study	Material	Duration (mo)	Defect depth (SD)	Duration (mo)	Defect depth (mm)	Measuring method
Brägger et al (1991)[36]	Silk	8	—	—	—	—
Günay et al (1991)[19]	Silk	1.5	—	—	—	—
Hickey et al (1991)[7]	Silk	1.5	4.45 mm	—	—	Probe
Jovanovic et al (1992)[21]	Silk	3	4.11 mm (0.95)	—	—	Intraoperative
Grunder et al (1993)[20]	Cotton	5	3.5 mm	—	—	Probe
Singh et al (1993)[22]	Silk	1.5	3 mm (0.92)	—	—	Intraoperative
Lang et al (1994)[36]	Silk	2/4	4.26 mm (0.65)	—	—	Probe
Schüpbach et al (1994)[23]	Cotton	3	30 to 50%	—	—	X-ray
Weber et al (1994)[38]	Silk	2	—	—	—	—
Cook and Rust-Dawicki (1995)[32]	Silk	1	2.1 mm (1.37)	—	—	Histology
		2	1.92 mm (1.13)	—	—	
		4	2.07 mm (0.92)	—	—	
		6	2.69 mm (1.27)	—	—	
Hürzeler et al (1995)[10]	Silk	3	4.2 mm (1.0)	—	—	Probe
Marinello et al (1995)[40]	Cotton	1-1.5	5.32 mm (0.2)	—	—	Histology
Warrer et al (1995)[37]	Cotton	9	0.96 mm 1.65%	—	—	Histology
Ericsson et al (1996)[39]	Cotton	1.5-2	20%	—	—	X-ray
Isidor (1996)[9]	Cotton	18	2.37 mm/(0.93)	18	5.56 (2.79)	Histology
Persson et al (1996)[24]	Cotton	1.5	20%	—	—	X-ray
Fritz et al (1997)[33]	Silk	6	1.72 mm (0.28)	—	—	X-ray
Hanisch et al (1997a)[25]	Cotton	10+1	—	—	—	Probe
Hanisch et al (1997b)[41]	Cotton	10+1	Max.:4.9 mm (1.6) Mand.:4.7 mm (2.5)	—	—	Probe
Hürzeler et al (1997)[11]	Silk	3	4.2 mm (1.0)	—	—	Intraoperative
Isidor (1997a)[16]	Cotton	18	2.37 mm (0.93)	18	5.56 (2.79)	Histology
Isidor (1997b)[35]	Cotton	18	2.37 mm (0.93)	18	5.56 (2.79)	Histology
Tillmanns et al (1997)[34]	Cotton	3/6	—	—	—	—
Eke et al (1998)[13]	Silk	6	—	—	—	—
Hürzeler et al (1998)[42]	Silk	4	2.3 mm (0.6)	4	1.3 (0.4)	Histology
Isidor (1998)[50]	Cotton	18	2.37 mm (0.93)	18	5.56 (2.79)	Histology
Miyata et al (1998)[43]	—	—	—	0.25 to 1.0	1.74 (0.11)	Histology
Tillmanns et al (1998)[14]	Cotton	3	2.19 mm (1.19)	—	—	Histology
		6	1.8 mm (1.15)	—	—	
Wetzel et al (1999)[26]	Silk	4	40%	—	—	X-ray

Another aspect that remains unclear is the effect of implant location. The only study investigating peri-implantitis in both the maxilla and mandible revealed no significant differences in the depth of the peri-implant defect.[25] On the other hand, the cortical structure of the mandible differs from the relatively cancellous maxillary bone,[44,45] so that the maxilla and mandible should at least demonstrate different susceptibility to overload-induced peri-implantitis. Further studies will be needed to clarify these unresolved questions.

The results of this literature study suggest that plaque is an etiologic factor for peri-implantitis; however, other or additional mechanisms cannot be excluded. The fact that all microbiologic studies carried out after successful induction of peri-implantitis by means of ligatures confirmed the presence of periodontally pathogenic microorganisms supports the plaque theory.[13,14,41] However, it is uncertain whether the peri-implant inflammatory response is really only the result of increased plaque accumulation or if the thread itself, as a foreign body, also acts as a stimulus. For example, plaque accumulation induced without the help of a thread resulted in mucositis, whereas plaque accumulation induced with a ligature led to peri-implantitis.[12] Bone resorption might occur in the immediate vicinity of the ligature as a response to the ligature. With an increasing distance between bone and the ligature, the osteolytic stimulus becomes weaker and the bone defect remains constant. However, the fact that similar defect depths were achieved in studies in which a new thread was regularly pushed into the bone defect counteracts this hypothesis.[10]

Treatment Methods

Treatment of peri-implantitis pursues 2 goals: to eliminate its causes and to restore the original condition. Ideally, the implant undergoes reosseointegration.

Table 6 Comparison of Studies of Experimental Peri-implantitis That Used Regenerative Treatment by Means of a Membrane, Augmentation, or a Combination of Both Measures

Study	Regenerative treatment	Ranking
Günay et al (1991)[19]	GBR, AB/HA	GBR > AB > HA
Grunder et al (1993)[20]	GBR	
Jovanovic et al (1992)[21]	GBR	
Singh et al (1993)[22]	GBR	
Schüpbach et al (1994)[23]	GBR	
Hürzeler et al (1995/1997)[10,11]	GBR, HA/DFDB, combination	HA > DFDB > GBR> HA+GBR > DFDB+GBR
Persson et al (1996)[24]	GBR	
Hanisch et al (1997a)[25]	rhBMP-2	
Wetzel et al (1999)[26]	GBR	

GBR = guided bone regeneration (ie, membrane); AB = autogenous bone; HA = hydroxyapatite; DFDB = demineralized freeze-dried bone; rhBMP-2 = recombinant human bone morphogenetic protein-2.

Conservative, resective, and regenerative treatment measures have been described, depending on the type and size of the bone defect.

In the few available studies investigating regenerative treatment of experimental peri-implantitis, the experimental model and the success of treatment varied considerably (Table 6). It was thus not possible to draw any consistent conclusions on the value of individual treatment methods. Methods described were placement of a membrane alone, filling of the defect with autogenous bone or a bone substitute material, and a combination of these 2 measures (Table 6).

Decontamination. Mechanical and chemical decontamination methods were available for cleaning of implant surfaces contaminated with bacteria and bacterial catabolites. Sandblasting units (Cavi Jet, De Trey, Dentsply, Dreieich, Germany; Prophy Jet, Dentsply, Encino, CA), either used alone[10,20,22,23] or in combination with a citric acid solution,[21,25] plastic brushes and sodium chloride,[19] chlorhexidine,[26] and delmopinol hydrochloric acid (Biosurface AB, Malmö, Sweden)[24] were used. In an in vitro study investigating the efficiency of different decontamination methods (polishing with distilled water/citric acid solution/0.12% chlorhexidine, sandblasting) on different implant surfaces,[46] only sandblasting resulted in successful decontamination of all surfaces. In an in vitro experiment, treatment with toluidine blue and subsequent irradiation with a diode soft laser with a wavelength of 905 nm for 1 minute also proved to be successful in the decontamination of differently structured titanium platelet surfaces (machine-polished, HA-coated, plasma-flame-sprayed, sandblasted, and etched) infected with *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Actinobacillus actinomycetemcomitans* prior to treatment.[47]

Membrane Technique. Guided bone regeneration (GBR) was carried out by means of non-resorbable e-PTFE membranes (Gore-Tex, W. L. Gore, Flagstaff, AZ). No studies are currently available on the value of resorbable membranes in the treatment of peri-implantitis. The membrane was placed in a submerged or a non-submerged manner (Table 7). In the submerged technique, the abutment was first removed, and the membrane was then placed over the implant in such a way that it overlapped the peri-implant bone margin by 2 to 3 mm. Finally, the mucoperiosteal flap was repositioned and closely adapted. In the non-submerged technique,[20,23] the membrane was placed around the abutment that had been left in situ. The membrane only was then covered with mucosa, while the abutment was allowed to perforate the mucosa.

Membranes were left in place for 1 to 5 months.[19,20,23,26] Half the studies reported premature membrane exposure[19–21,26] occurring between the second and third postoperative week and necessitating removal of the membrane in case of inflammation of the peri-implant tissue (Table 7).[19,20,26] If the exposed membrane was not removed, reduced bone growth was observed, compared with membranes undergoing uneventful healing.[21] The cause of this complication, which occurs in a great number of implants, is still unknown. No common factors were found in the studies concerned. In all studies in which a membrane was placed in a non-submerged manner,[20,23] only connective tissue sheathing of the implants was achieved. In a comparative study by Grunder et al,[20] no significant difference in bone

Table 7 Comparison of Results Achieved with Regenerative Treatment with Non-Resorbable Membranes of Experimentally Induced Peri-implantitis

		Membrane			Treatment result	
Study	Implant type	Technique	Application time (mo)	Complications	Bone gain	Reosseointegration
Günay et al (1991)[19]	S/U	Submerged	1	Exposure + removal	Yes	Yes
Jovanovic et al (1992)[21]	S/U	Submerged	2/4.5	Exposure	Yes	No
	C/TPS				Yes	No
	C/HA				Yes	Yes
Grunder et al (1993)[20]	S/U	Submerged	1	Exposure + removal	–0.1 mm (SD 0.1)	No
		Non-submerged	1		–0.1 mm (SD 0.2)	No
Singh et al (1993)[22]	S/U	Submerged	1.5		2.13 mm	35.6% (0.76 mm)
Schüpbach et al (1994)[23]	S/U	Non-submerged	1		No	No
Hürzeler et al (1995/1997)[10,11]	S/U	Submerged	4		2.5 mm (SD 0.3)	1 mm (SD 0.2)
Persson et al (1996)[24]	S/U	Submerged	4		No	No
Wetzel et al (1999)[26]	C/U	Submerged	5	Exposure + removal	2.2 mm (SD 1.17)	2% (0.07 mm; SD 0.14)
	C/TPS				2.6 mm (SD 0.69)	13.6% (0.34 mm; SD 0.34)
	C/SLA				2.3 mm (SD 0.86)	19.7% (0.6 mm; SD 0.29)

S = screw-shaped; C = cylindric; U = uncoated; TPS = titanium plasma flame-sprayed; HA = hydroxyapatite-coated; SLA = sandblasted and acid-etched.

gain was observed between submerged and non-submerged membrane placement; however, in contrast to other studies,[10,11,19,21,26] the authors achieved no treatment success with the submerged technique.

Guided Bone Regeneration Alone. When the success of treatment is evaluated, a distinction must be made between bone gain and reosseointegration. Bone gain describes reduction of the peri-implant bone defect, whereas reosseointegration is defined as renewed intimate contact of bone with the previously contaminated implant surface and is determined by histology and histomorphometric findings.

In 2 studies, both significant bone gain and satisfactory reossification values were achieved.[11,22] By leaving membranes in place for 6 weeks, Singh et al[22] achieved a mean bone gain of 2.13 mm and reosseointegration of 35.6% (0.76 mm) in pigs; Hürzeler et al[11] found a bone gain of 2.5 mm (SD 0.3 mm) and reosseointegration of 1.0 mm (SD 0.2) in dogs after 4 months of membrane application. Both studies used uncoated screw-type implants.

Jovanovic et al,[21] who tested different types of implants, were able to achieve clear bone gains in all types of implants, but reported satisfactory reosseointegration values only for HA-coated cylindric implants. However, they did not provide any concrete data about bone gain and reosseointegration. Wetzel et al,[26] who tested the treatment using cylindric implants with varying surface features, achieved above-average bone gains of up to 2.6 mm but almost no reosseointegration.

The effect of implant surface on bone gain and reossification is still unclear. A comparison of the individual studies seems to indicate that uncoated smooth screw-type implants (Brånemark) are most suitable for GBR.[10,11,22] On the other hand, Jovanovic et al[21] achieved greater bone gains and higher reossification values with HA-coated cylindric implants than with uncoated screw-type implants. Wetzel et al[26] reported favorable bone gains using uncoated rough and coated cylindric implants but did not achieve any satisfactory reosseointegration (Table 7). This effect of surface composition on the success of treatment might be related to the achievable effect of decontamination measures. Most likely, coated implants and rough surfaces might not be decontaminated as easily as implants with smooth surfaces.

In those studies in which GBR was used without success,[20,23,24] connective tissue sheathing of the implants occurred. The causes of this treatment failure are unclear. The only discernible difference between the successfully and the unsuccessfully treated defects was that the peri-implant bone defects in 2 of the unsuccessful studies were mainly horizontal,[20,23] while the defects treated in all other studies were primarily vertical defects. Presumably, circular defects cannot be adequately treated by means of GBR.[48]

Augmentation. Grafting materials used were either autogenous bone[19] or a bone substitute material. Available bone substitute materials were HA,[10,19] demineralized freeze-dried bone (DFDB),[10] and

Table 8 Comparison of Different Grafting Materials in the Regenerative Treatment of Experimentally Induced Peri-implantitis

Study	Grafting material	Duration (mo)	Bone gain	Reosseo-integration
Günay et al (1991)[19]	AB	3	Yes	Yes
	HA	3	No	No
Hürzeler et al (1995)[10]	DFDB	5	1.6 ± 0.7 mm	0.9 ± 0.3 mm
	HA	5	1.3 ± 0.6 mm	0.9 ± 0.4 mm
Hanisch et al (1997a)[25]	rhBMP-2	4	2.6 ± 1.2 mm	29% ± 10.5%

AB = autogenous bone; HA = hydroxyapatite; DFDB = demineralized freeze-dried bone; rhBMP-2 = recombinant human bone morphogenetic protein-2.

recombinant human bone morphogenetic protein-2 (rhBMP-2)[25] (Table 8). When autogenous bone was compared with HA (Interpore 200, macroporous HA granular powder, Interpore International, Irvine, CA), the autogenous bone graft was superior to HA.[19] When HA and DFDB were compared to each other, DFDB was slightly superior to HA.[10,11] After a 5-month observation period, DFDB resulted in a mean bone gain of 1.6 mm (SD 0.7) and HA showed a mean bone gain of 1.3 mm (SD 0.6). In both cases, reosseointegration of 0.9 mm (SD 0.3) was achieved.

Augmentation with rhBMP-2 resulted in a vertical bone gain of 2.6 mm (SD 1.2) and 29% reosseointegration (SD 10.5).[25] This material seems to have great potential to support new bone formation and reosseointegration in advanced peri-implantitis defects around HA-coated dental implants in monkeys (Table 8). Grafting materials and membranes, when used alone, seem to result in a similar degree of reosseointegration.[11] However, as far as bone gain without actual reosseointegration is concerned, direct comparison of both methods demonstrated that GBR yields markedly better results.[11,19]

Guided Bone Regeneration + Grafting. One study examined a combination of GBR and augmentation measures (DFDB and HA), which yielded the most favorable results of all applied treatment methods.[10,11] In single use as well as in combination with GBR, DFDB provided greater bone gain (3.0 ± 0.5 mm, DFDB+GBR) than HA used in combination with a membrane (2.4 ± 0.4 mm). The combined treatment was practically equal to GBR alone in terms of bone gain, but was significantly superior to GBR in terms of reosseointegration. No other treatment method achieved reosseointegration values of 2.3 ± 0.6 mm (HA + GBR) and 2.2 ± 0.4 mm (DFDB + GBR).

SUMMARY

This literature review summarizes the model of experimental peri-implantitis and available regenerative treatment methods. For this purpose, studies in which experimental peri-implantitis was induced in animals were compared and examined for consistent and inconsistent findings. Because of the multitude of applied experimental models, no uniform statement could be made about the induction and treatment of experimental peri-implantitis. For example, only one third of the available studies met the criteria required for a statistical evaluation. This limitation of a relatively small number of studies reduces the indicative value of the results obtained and makes further statistical analyses nearly impossible. An evaluation of the individual treatment methods is possible to a limited degree for the same reason.

This review did not evaluate different diagnostic methods, since a detailed review of the respective literature is already available.[3,4]

As far as possible, the evaluation of treatment methods showed that removal of granulation tissue and decontamination of the implant surface alone were not very effective.[26] This method only resulted in a minimum reduction of the bone defect. However, the result achieved bears no relationship to the effort and cost involved in a surgical procedure.

Of the treatment methods described, the combination of GBR and filling of the defect with DFDB or HA proved to be most effective, followed by GBR alone, and then augmentation with autogenous bone or a bone substitute material alone. No study is currently available on the treatment of experimental peri-implantitis with a combination of autogenous bone and GBR, although this method has been used successfully in clinical studies.[49]

There is a question as to whether the different bone quality of and blood supply to the maxilla and the mandible play a role in the treatment of peri-implantitis. Since no generally valid treatment scheme has been established in clinical practice to date, further clinical and experimental studies of peri-implantitis based on a standardized experimental model are needed.

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