

Microbiota Around Root-Form Endosseous Implants: A Review of the Literature

Kees Heydenrijk, DDS, PhD¹/Henny J. A. Meijer, DDS, PhD²/Wil A. van der Reijden, PhD¹/
Gerry M. Raghoebar, MD, DDS, PhD²/Arjan Vissink, MD, DDS, PhD²/Boudewijn Stegenga, DDS, PhD²

Although high success rates for root-form endosseous implants have been reported, failures occasionally occur, and these implants must be removed. At least 10% of the failures have been suggested to be the result of peri-implantitis. There is some evidence that periodontal pathogens, mainly those belonging to the group of Gram-negative anaerobic rods, play a role in the etiology of peri-implantitis. This article provides an overview of the literature associated with common peri-implant microbiology and an assessment as to whether bacteria associated with periodontitis exert a possible risk for peri-implant tissue breakdown. The peri-implant area is colonized by a large variety of oral microbial complexes. The microflora of the oral cavity prior to implant placement determines the composition of the microflora in the peri-implant area. Implants involved in peri-implantitis are colonized with large amounts of Gram-negative anaerobic bacteria, including Fusobacteria, spirochetes, Bacteroides forsythus, and "black-pigmented bacteria" such as Prevotella intermedia, Prevotella nigrescens, and Porphyromonas gingivalis. Also, Actinobacillus actinomycetemcomitans can be isolated from these lesions. Thus, the microflora of peri-implantitis lesions resembles that of adult or refractory periodontitis. However, the presence of periodontal pathogens does not always lead to a destructive process. Therefore, the etiologic role of specific microorganisms in implant failure related to infection is still not resolved. Controversy remains as to whether organisms recovered from the original microflora cause the failure (and if so to what extent) or merely result from the infection. Nevertheless, there is accumulating evidence that bacteria cause the disease, while the individual's genetic makeup and environmental influences determine the severity of the disease. (INT J ORAL MAXILLOFAC IMPLANTS 2002;17:829-838)

Key words: dental implants, microbiology, peri-implantitis, periodontology

Root-form endosseous implants are commonly used for the fixation of prosthetic restorations. Brånemark and coworkers¹ were the first to describe the anchorage of dental prostheses by osseointegrated dental implants. Over the years,

many different implant systems have been introduced, and the indications for their application have gradually been extended. Although high success rates have consistently been reported for many implant systems,² failures leading to implant removal still occur. The overall failure rate for Brånemark System implants (Nobel Biocare, Göteborg, Sweden) is 7.7% over a 5-year period.³ Failure rates in the edentulous maxilla and mandible are 10% and 3%, respectively, while in partially edentulous patients 4% of the implants are lost.³ Comparable failure rates have been reported for other implant systems.²

To achieve consensus on terminology, *implant failure* has been defined as the inadequacy of the host tissue to establish or to maintain osseointegration,³ and *peri-implantitis* has been defined as the inflammatory process affecting the tissue around an

¹Assistant Professor, Department of Oral and Maxillofacial Surgery and Maxillofacial Prosthetics, University Hospital Groningen, The Netherlands.

²Associate Professor, Department of Oral Biology, Section of Clinical Periodontal Microbiology, Academic Center for Dentistry Amsterdam, The Netherlands.

Reprint requests: Dr Kees Heydenrijk, University Hospital Groningen, Department of Oral and Maxillofacial Surgery and Maxillofacial Prosthetics, P. O. Box 30001, 9700 RB Groningen, The Netherlands. Fax: +31503612831. E-mail: k.heydenrijk@kchir.azg.nl

osseointegrated implant in function, resulting in loss of supporting bone.⁴

Failing implants are characterized by loss of supporting bone and mobility. Patients experience spontaneous pain as well as pain on clenching, percussion, or palpation, and deep pockets may be present. Referring to the occurrence in time, *early* and *late* failures can be distinguished. In *early failure*, osseointegration has never been established, thus representing an interference with the healing process. Early failures occur prior to prosthetic rehabilitation.³ Surgical trauma, insufficient quantity or quality of the bone surrounding the implant, premature loading of the implant, and bacterial infection have been implicated as causes for early implant failure.^{5,6} In *late failure*, the established osseointegration is not maintained, implying processes involving loss of osseointegration. Late failures occur following prosthetic rehabilitation.³ Late failures can be divided into 2 subgroups, with one including implants failing during the first year of loading ("soon" late failures) and one including implants failing in subsequent years ("delayed" late failures). Each makes up about 50% of the late failures. It seems reasonable to attribute most of the "soon" late failures to overloading in relation to poor bone quality and insufficient bone volume. The "delayed" late failures probably can be attributed to progressive changes of the loading conditions in relation to bone quality and volume and peri-implantitis.^{6,7}

There is evidence supporting the view that periodontal pathogens, mainly those belonging to the group of Gram-negative anaerobic rods, play an important role in developing peri-implantitis. In this article, this evidence is reviewed against the background of the current knowledge of the common peri-implant microbiology.

This article provides a comprehensive review of studies published in the international peer-reviewed literature published in English concerning the subgingival microflora surrounding root-form endosseous oral implants in humans. Using MEDLINE (US National Library of Medicine), a literature search was performed on articles published between January 1980 through December 2000. Key words used in the search were: dental, implants, microorganisms, microbiota, microbiology, microflora, peri-implantitis, failure, periodontology, periodontitis, and genetic. Publications presented in abstract form and animal studies were ignored. All resulting papers were analyzed for their contents and included if appropriate. Because of major differences between study designs and/or methodologic shortcomings, it was not possible to

execute a meta-analysis that includes a sufficient number of studies.

MICROBIAL COLONIZATION OF THE MOUTH WITHOUT IMPLANTS

It has been estimated that about 400 different microbial species are capable of colonizing the dentate oral cavity and that any individual may harbor over 150 different species.³ Samples from the healthy gingival sulcus contain relatively few (10^3 to 10^6) cultivable organisms, predominantly consisting of Gram-positive cocci and rods, principally *Actinomyces naeslundii* (14%), *Actinomyces gerencseriae* (11%), *Streptococcus oralis* (14%), and *Peptostreptococcus micros* (5%).⁹⁻¹² Gram-negative anaerobic rods account for 13% of the total cultivable organisms on average. Many of the suspected periodontal pathogens belong to this anaerobic group, indicating that colonization with putative periodontal pathogens in healthy subjects without signs of gingival inflammation is possible.¹⁰

Subgingival bacterial counts range up to more than 10⁸ in deep periodontal pockets. There is general agreement that periodontitis is an infectious disease associated with only a few of the bacterial species found in dental plaque.¹³ With the development of periodontitis, there is a shift toward a subgingival flora containing a higher proportion of Gram-negative rods and decreased proportions of Gram-positive species. In an established periodontal lesion, low numbers of cocci and high numbers of motile rods and spirochetes are seen. Increased proportions of *Porphyromonas gingivalis*, *Bacteroides forsythus*, and species of *Prevotella*, *Fusobacterium*, *Campylobacter*, and *Treponema* have been detected.^{11,12} *P. gingivalis* was isolated in 79% of periodontitis patients.¹⁴ However, it is still unknown whether the presence of the Gram-negative bacteria is secondary to altered nutritional and anaerobic conditions because of the inflammatory processes and pocket formation or is itself responsible for the periodontal destruction.⁹ To become associated with destructive periodontitis, the microorganisms must comply with several criteria⁸:

- The species should be found more frequently and in higher proportions in cases of infection compared to non-diseased sites (association).
- Absence of the species should be accompanied by a parallel remission of disease (elimination).
- Production of antibodies or cellular immune response is directed specifically at that species (host response).

- Potentially damaging metabolites are produced or properties possessed by a species (virulence factors).
- Periodontal disease progression conferred by the presence of a species at a given level is evaluated in a prospective study (risk assessment).

On the basis of these criteria, several species have been related to the etiology of destructive periodontal diseases, of which *Actinobacillus actinomycetemcomitans* and *P gingivalis* have the strongest association. *A actinomycetemcomitans* is the most important microorganism in juvenile periodontitis, while *P gingivalis* is considered to be associated with adult periodontitis and refractory periodontitis. In low numbers, *Prevotella intermedia* and *Prevotella nigrescens* have been found in periodontally healthy subjects, but they may also be associated with the development of periodontitis. To affect periodontal tissues, these species probably must persist in the subgingival area at elevated levels over extended periods of time. Furthermore, *B forsythus* is found more frequently in periodontal patients, and its levels are related to probing depth and periodontal breakdown.^{11,12,15} Other bacteria associated with periodontal destruction include *Fusobacterium nucleatum*, *Campylobacter rectus*, *P micros*, *Treponema denticola*, and *Treponema vincentii*. Like *P intermedia*, these species are probably opportunistic pathogens with relatively low pathogenic potential and have to colonize the subgingival area for longer periods of time at elevated levels to be able to affect the periodontium.

Most of the above-mentioned periodontal pathogens are Gram-negative anaerobic rods. It is, therefore, not surprising that during the development of periodontitis, there is a shift toward a subgingival flora containing relatively more Gram-negative rods and fewer Gram-positive species.

Following full-mouth tooth extraction, changes occur in the tissues and/or surfaces that are available for microorganism adherence. When patients with severe periodontitis become edentulous, *A actinomycetemcomitans* and *P gingivalis* are no longer detectable within a month after full-mouth tooth extraction, suggesting that their primary habitat is the dentition or the periodontal sulcus.¹⁶ Furthermore, a marked reduction or even elimination of spirochetes, as well as a reduction in lactobacilli, yeasts, *Streptococcus mutans*, and *Streptococcus sanguis* occurs in edentulous adults with or without conventional removable dentures compared to dentate patients.¹⁷ It seems that no significant periodontopathic flora capable of constituting a risk factor or reservoir for transmission,¹⁶ eg, when implants will be placed, is left following full-mouth tooth extraction.

MICROBIOTA AROUND STABLE IMPLANTS

In edentulous patients, the subgingival area around implants consists mainly of Gram-positive facultative cocci and non-motile rods. On clinically stable implants, *S sanguis* and *Streptococcus mitis* are the most predominant organisms, while motile rods, spirochetes, fusiforms, and filaments are infrequently found.¹⁸ *A actinomycetemcomitans* and *P gingivalis* are seldom detected, whereas *P intermedia* and *P nigrescens* are more common. The peri-implant flora in edentulous patients is comparable to the flora colonizing oral soft tissues of denture-wearing edentulous patients without implants and the subgingival flora of periodontally healthy dentate patients.^{19–23} Furthermore, the peri-implant microbiota is established quite soon after implant placement, and significant subsequent shifts do not occur.^{21,24} These data show that the microflora is stable in healthy patients, comprising a microbiota in which periodontal pathogens are present only at low or below detectable levels.

In partially edentulous patients, the total number of peri-implant microorganisms is increased, and the proportion of motile rods, spirochetes, and cocci is increased when compared to edentulous patients.^{25–28} Quirynen and coworkers²⁸ isolated the periodontal pathogens *P intermedia/P nigrescens*, *A actinomycetemcomitans*, and *P gingivalis* in 9 (26%), 1 (3%), and 1 (3%) of their sample of partially edentulous patients, respectively, and in none of the edentulous patients. More specifically, they observed that the proportion of spirochetes and motiles around the implants had increased at the expense of the proportion of cocci, if the flora of the remaining teeth harbored more than 20% spirochetes.

The concept that the composition of the subgingival microflora around implants in partially edentulous patients is a resultant of the composition of the flora around the teeth has been confirmed in other studies.^{28–38} Thus, the peri-implant microflora in partially edentulous patients seems to depend on the periodontal flora of the remaining dentition. As in edentulous patients, colonization of the implant sites with flora specific for that patient occurs soon after the implants are in contact with the oral environment, without major changes over time.^{27,32,39–43} However, Kalykakis and associates⁴³ and Papaioannou and colleagues²⁷ have reported some time-dependent changes in the peri-implant flora. Papaioannou and colleagues²⁷ reported an increase in the proportion of motile rods and spirochetes at the expense of cocci around implants. Kalykakis and associates⁴³ reported an increase with time in the number of putative periodontal

Table 1 Studies Evaluating the Microbiota of the Peri-implant Area of Failing Implants

Publication	Study design	No. of patients	Implants		Time of failure (mo)	Results
			No.	Type		
Mombelli et al ⁴⁶	Retrospective	7 (E + PE)	8	ITI	ND	Failing implants harbored a flora similar to adult periodontitis with increased proportions of <i>P intermedia</i> , <i>Fusobacterium</i> spp, and spirochetes. <i>P gingivalis</i> was not isolated
Mombelli et al ²¹	Prospective	1 (E)	1	ITI	0 to 4*	Chronologically, increased proportions of <i>Actinomyces odontolitus</i> followed by <i>Fusobacterium</i> spp and spirochetes were found around the failing implant
Alcoforado et al ⁴⁴	Retrospective	12 (E + PE)	18	5 different	ND	A great diversity in the microbial composition with oral as well as primarily non-oral organisms was isolated around the different failing implants
Malmstrom et al ⁴⁸	Retrospective	1 (PE)	4	Brånemark	0 to 2*	<i>C rectus</i> , <i>F nucleatum</i> , and <i>E corrodens</i> were associated with implant failure in a patient with rapidly progressive periodontitis
Quirynen et al ²⁵	Retrospective	4 (E + PE)	4	Brånemark	ND	Implants failing due to overload demonstrated a flora similar to periodontal health, while implants failing due to infection were colonized by a periodontopathic flora
Rosenberg et al ⁵¹	Prospective	5 (PE), 6 (E)	32	4 different	2 to 18 **	In implants failing with infection, many suspected periodontopathic organisms constituted high proportions of the cultivable microflora, while implants failing from suspected traumatic influences demonstrated a flora similar to periodontal health
Rams et al ⁴⁵	Retrospective	1 (PE)	1	Tri-Stage	10**	High proportions of <i>Fusobacterium</i> spp and <i>Peptostreptococcus prevotii</i> were isolated in the failing implant
Listgarten and Lai ⁴⁷	Retrospective	41 (ND)	41	ND	ND	High incidence of <i>B forsythus</i> , spirochetes, <i>Fusobacterium</i> spp, <i>P micros</i> , and <i>P gingivalis</i>
Van Winkelhoff et al ⁴²	Prospective	1 (PE)	2	Brånemark	0 to 12**	Implant loss was associated with high levels of <i>P gingivalis</i>

E = edentulous; PE = partially edentulous; ND = not defined. *After implant placement; **After implant loading. Brånemark implants: Nobel Biocare, Göteborg, Sweden; ITI: Straumann Institut, Waldenburg, Switzerland; Tri-Stage: San Diego, CA.

pathogens, such as *P gingivalis*, *A actinomycetemcomitans*, or *P intermedia*. Because of the retrospective nature of latter studies, the authors executed cross-sectional statistics and only limited conclusions can be drawn. The true time effect can only be judged based on sufficiently large prospective longitudinal studies.³⁹⁻⁴² It is generally assumed that no significant changes in the oral microbiota occur in the long term and that present (potential) pathogens do not necessarily act in a peri-implant pathogenic manner.^{39,40}

It has been suggested that differences in the microbiota might occur as the result of various implant characteristics (ie, material, coating, roughness, shape).³ However, studies by Alcoforado and coworkers,⁴⁴ Rams and associates,⁴⁵ Mombelli and coworkers,³⁰ and Lee and colleagues³⁵ could not

relate the presence of particular microorganisms to a particular implant system. Thus, although only limited data are available comparing the microflora of different implant systems, the implant type and surface roughness do not seem to be of significance in the peri-implant microflora.

MICROBIOTA AROUND FAILING IMPLANTS

A wide variety of microorganisms can be cultivated from the peri-implant region of failing root-form endosseous implants in edentulous and partially edentulous patients. Implant failure cannot be related to a specific microorganism, but certain bacteria are present more frequently around failing implants (Table 1).

Mombelli and associates⁴⁶ isolated an increased proportion of Gram-negative anaerobic rods in edentulous and partially edentulous patients, especially *P intermedia*, *Fusobacteria*, and spirochetes. Alcoforado and coworkers⁴⁴ observed high proportions of *P micros*, *P intermedia*, *C rectus*, and *Fusobacterium* species. Listgarten and Lai⁴⁷ isolated *B forsythus* (59%), spirochetes (54%), *Fusobacterium* (41%), *P micros* (39%), and *P gingivalis* (27%) around many of the failing implants in partially edentulous patients. Van Winkelhoff and colleagues⁴² evaluated the microflora of periodontal pockets and the peri-implant sulcus in 20 partially edentulous patients on 4 occasions, ranging from implant placement up to 1 year after loading. Preoperatively, *P gingivalis* was isolated in 3 patients. In 1 of these patients, 2 implants were lost within 12 months after abutment connection because of the loss of osseointegration. In this prospective study, the authors suggested that *P gingivalis* might have played a role in this implant failure, although this observation is rather casuistic.

The results of the aforementioned studies suggest similarities between the microbiota around failing implants and the microbiota associated with periodontitis. Because totally edentulous patients often lack potential periodontal pathogens, which are more common in dentate patients, it is of great interest to compare the microbiota around failing implants in edentulous and partially edentulous patients. Unfortunately, in only 1 study were the microbiota of a failing implant in an edentulous patient reported.²¹ Other studies evaluating the microbiota of failing implants included edentulous as well as partially edentulous patients, but the authors did not describe their observations for each separate patient group. Therefore, the incidence or the pattern of failure in edentulous and partially edentulous patients cannot be compared. Also, the question as to whether peri-implantitis is more common in either partially edentulous or edentulous patients remains unanswered. The latter information might provide a clue in resolving the discussion as to whether the actual oral microbiota is the cause or the result of peri-implantitis.

Malmstrom and coworkers⁴⁸ and Fardal and associates⁴⁹ concluded that implants placed in patients with a history of refractory (recurrent) periodontitis probably are at increased risk of failure, presumably because the chance to harbor potential periodontal pathogens is higher. The distressing results of these 2 case reports can easily lead to the hypothesis that implant placement is contraindicated in patients with (a history of) refractory periodontitis. However, this is not sup-

ported by larger studies in these periodontal patients, which report success rates exceeding 90%.^{40,45,50} In a study by Leonhardt and colleagues,⁴⁰ 19 dentate periodontal patients were followed for 3 years after implant placement. Preoperatively, more than 30% of the patients were colonized with *A actinomycetemcomitans* or *P gingivalis*, and nearly all patients harbored *P intermedia*. Within 1 month after implant placement, these microorganisms were found around most implants, but at the 3-year evaluation, peri-implant marginal bone loss exceeding 0.5 mm was observed in only 1 patient. These results suggested that the presence of periodontal pathogens does not necessarily result in the development of peri-implantitis, but the presence of other co-factors is required as well. Thus, local or systemic circumstances are needed to give the supposed periodontopathic microorganism the opportunity to become really pathogenic and causative for infection.

Quirynen and Listgarten²⁵ and Rosenberg and coworkers⁵¹ observed significant differences in the peri-implant flora in patients with failures related to infection or associated with traumatic overloading. In patients with failing implants related to infection, many spirochetes and motile rods could be cultivated, while the peri-implant flora of implants failing caused by overloading resembled that of subjects with poor periodontal health. It seems realistic to conclude that it is possible to place implants with acceptable success rates in periodontal patients as long as the number of potential periodontal pathogens is kept at a low level⁴⁰ and other potential (co-)factors are within normal limits.

EFFECT OF MUCOSAL CLINICAL VARIABLES AND PERI-IMPLANT BONE LEVEL ON THE MICROFLORA

For teeth, clinical parameters such as Plaque Index, Bleeding Index, Gingival Index, and probing pocket depth are positively correlated with the presence of suspected periodontal pathogens.⁵² It is of interest to note that comparable associations have been reported for dental implants in several studies. Positive correlations have been found between the Bleeding Index and the proportion of motile organisms²⁷ and also between probing pocket depth and the composition of microflora (Table 2).^{24,26-28,34,35,53-57} In other studies, however, no such associations were established.^{30,37,58-60} Although suspected periodontal pathogens were identified at implant sites in these studies, the clinical parameters were not indicative of deteriorating

Table 2 Studies Evaluating the Correlation Between Clinical Parameters and the Peri-implant Microflora

Publication	Study design	No. of patients	Implants		Time of sampling	Results
			No.	Type		
Lekholm et al ⁵⁴	Retrospective	20 (E + PE)	125	Brånemark	0.5 to 12 y	Deeper pockets were correlated with increasing presence of spirochetes
Sanz et al ⁵³	Retrospective	13 (PE)	13	ESCI	ND	Pathogens associated with active periodontitis lesions were detected in higher frequencies and percentages in implants with pockets ≥ 4 mm, GI ≥ 2 , or CFF ≥ 40
Mombelli and Mericske-Stern ²⁴	Prospective	18 (E)	36	ITI	2 to 3 y	The relative proportion of <i>Capnocytophaga</i> was related to PPD and bleeding
Rams et al ⁴⁵	Retrospective	9 (PE)	40	Tri-Stage	7 to 10 mo	Increased PPD was related to decreased proportion of cocci and increased proportion of motiles. Pockets > 7 mm harbored more <i>Fusobacterium</i> spp and <i>P. prevotii</i> (1 patient)
Palmisano et al ⁵⁵	Retrospective	25 (E + PE)	43	Integral	> 1 y	PPD was positively correlated with spirochetes and negatively correlated with cocci
Dharmar et al ²⁶	Retrospective	24 (E + PE)	64	Brånemark	ND	PPD was positively correlated with motile rods and negatively correlated with cocci
Papaoiannou et al ²⁷	Retrospective	297 (E + PE)	561	Brånemark	1 to 120 mo	PPD was positively correlated with spirochetes, fusiforms, and filaments and negatively correlated with cocci. BOP was positively correlated with motile rods
Quirynen et al ²⁸	Retrospective	159 (PE)	300	Brånemark	1 to 11 y	Samples from peri-implant pockets ≥ 4 mm showed increased proportions of spirochetes and motiles
Danser et al ⁵⁷	Retrospective	20 (E)	91	Brånemark IMZ	1 to 12 y	Subjects harboring <i>P. intermedia</i> showed pockets ≥ 5 mm
Tanner et al ⁵⁶	Retrospective	12 (ND)	12	ND	ND	Implants with deeper probing depths or increased bone loss were frequently colonized by <i>B. forsythus</i> , <i>F. nucleatum</i> , and <i>C. rectus</i>
Keller et al ³⁴	Retrospective	15 (PE)	60	ITI	0.5 to 5 y	<i>C. rectus</i> was found more frequently in pockets ≥ 4 mm. <i>P. gingivalis</i> , <i>Selenomonas</i> spp, <i>P. melaninogenica</i> , and <i>A. naeslundii</i> were only isolated from pockets ≥ 4 mm

E = edentulous; PE = partially edentulous; ND = not defined; GI = Gingival Index; CFF = crevicular fluid flow; PPD = probing pocket depth; BOP = bleeding on probing. Brånemark: Nobel Biocare, Göteborg, Sweden; ESCI: endosteal sapphire ceramic implant; ITI: Straumann Institut, Waldenburg, Switzerland; Tri-Stage: San Diego, CA; Integral: Calcitek, Carlsbad, CA; IMZ: Friedrichsflod, Mannheim, Germany.

support or implant failure. This supports the hypothesis that co-factors are required for periodontopathic bacteria to become pathogenic.

Probing pocket depth has been found to be the most important clinical parameter in relation to the peri-implant microbiota.⁴⁵ With increasing pocket depth, a significant decline in cocci and increase of other morphotypes (motiles and spirochetes), as well as for the total number of organisms, was observed.⁴⁵ Other clinical parameters seem to be less significant in relation to the peri-implant microbiota.

Few studies have reported on the microbiota of implants with peri-implant bone defects (Table

3).^{32,38,40,61-63} Again, these bone defects could not be related specifically to the presence of certain microorganisms, but certain microorganisms were detectable or present at higher levels in peri-implant bone defects. Mengel and associates³² did not find any correlation between the subgingival microflora and peri-implant marginal bone loss, while other authors reported some correlations. Frequently, *P. intermedia*, *P. gingivalis*, *A. actinomycetemcomitans*, *B. forsythus*, *T. denticola*, *P. nigrescens*, *P. micros*, and *F. nucleatum* were isolated in implants showing bone defects.^{38,40,60-62} Again, co-factors seem to be required for periodontopathic bacteria to be associated with peri-implant bone loss.

Table 3 Studies Evaluating the Correlation Between Marginal Bone Loss and the Peri-implant Microflora

Publication	Study design	No. of patients	Implants		Time of sampling	Results
			No.	Type		
Leonhardt et al ⁴⁰	Prospective	19 (PE)	63	Brånemark	0 to 36 mo	At the 3-year evaluation, 3 implants in 1 patient showed bone loss > 0.5 mm. These implants were colonized with <i>P intermedia</i>
Mengel et al ³²	Prospective	5 (PE)	36	Brånemark	12 mo	No correlation was found between the subgingival microflora and peri-implant marginal bone loss
Augthun and Conrads ⁶¹	Retrospective	12 (E)	18	IMZ	6 y	All implants showed bone loss exceeding 5 mm. Most implants were colonized by <i>A actinomycetemcomitans</i> and <i>Prevotella</i> spp
Salcetti et al ⁶²	Retrospective	29 (E + PE)	69	ND	> 1 y	Implants showing > 2 mm bone loss harbored more frequently <i>F nucleatum</i> , <i>P micros</i> , and <i>P nigrescens</i>
Leonhardt et al ⁶³	Retrospective	88 (E + PE)	ND	Brånemark	5 to 7 y	Implants with bone loss ≥ 3 threads after the first year of loading were frequently colonized by <i>P gingivalis</i> , <i>P intermedia</i> , or <i>A actinomycetemcomitans</i> . <i>Staphylococcus</i> spp, enterics, and <i>Candida</i> spp were also found frequently
Hultin et al ³⁸	Retrospective	15 (PE)	55	Brånemark	10 y	Five implants showed bone loss > 2 mm. These implants were colonized by <i>A actinomycetemcomitans</i> , <i>P gingivalis</i> , <i>P intermedia</i> , <i>B forsythus</i> , and <i>T denticola</i>

E = edentulous; PE = partially edentulous; ND = not defined.

The peri-implant tissues of dental implants are colonized by a large variety of oral microbial complexes. The microflora that is present in the oral cavity before implant placement determines the composition of the newly establishing microflora around implants. Implants with signs of deterioration (peri-implantitis) show a microbiota resembling that of adult or refractory periodontitis. These implants yield large amounts of Gram-negative anaerobic bacteria, with *Fusobacteria*, spirochetes, *B forsythus*, and "black-pigmenting bacteria" such as *P intermedia* and *P nigrescens*. *P gingivalis* and *A actinomycetemcomitans* are infrequently cultivated putative periodontal pathogens. It is controversial as to whether the recovered organisms are the cause of the failure or whether the actual microbiota is merely a result or a manifestation of changed intraoral circumstances. It has been shown that periodontal pathogens can be present in the subgingival area around implants for a long period of time without resulting in signs of destructive processes or implant failure. Moreover, when peri-implantitis is present around 1 of multiple implants in the same patient, the other implants (which are exposed to the same oral environment) do not necessarily show signs of deterioration. Therefore, the role of oral microbiota in implant failure is subject to discussion.⁷

Local circumstances (ie, unsatisfactory oral hygiene, bone defects, deep pockets, overload) as well as systemic conditions (ie, diabetes, smoking, genetic factors) may be important contributing factors as well. This is in agreement with the current periodontal literature, in which it is increasingly emphasized that systemic factors play a role in the development of periodontitis.⁶⁴⁻⁶⁶ The known periodontal pathogens are linked to periodontitis in different ways. *A actinomycetemcomitans* and *P gingivalis* seem to play a primary role in the development of periodontitis.^{11,14,67} However, these microorganisms are found infrequently in peri-implantitis. Other periodontal pathogens play a secondary role in the development of periodontitis. They must be present in high numbers, or a co-factor is required for these pathogens to come to expression.¹¹

Therefore, the following hypothesis is postulated. Microorganisms have the potential to act as promoters or catalysts in implant failure, but they need a suitable oral environment to do so. In other words, favorable local circumstances or systemic conditions are required to allow microorganisms to become pathogenic. Since *A actinomycetemcomitans* and *P gingivalis* are infrequently found in peri-implantitis patients and other periopathogens are thought to be less pathogenic, local circumstances

Table 4 Summary of the Main Conclusions Derived from the Comprehensive Review of the Literature

Conclusion	References
The microflora of the oral cavity prior to implantation determines the composition of the flora in the peri-implant area	28–38
The microflora around stable implants resembles that of the subgingival flora of healthy dentate patients	19–23
The microflora of peri-implantitis lesions resembles that of adult or refractory periodontitis	21, 25, 42, 44–46, 51
Potential periodontal pathogens present in the oral cavity do not necessarily act as peri-implant pathogens	39–41, 45, 50
The etiology of peri-implantitis probably is multifactorial, and genetic factors play an important role	64, 65, 68

and systemic conditions are probably more important in implant failure than the presence of periopathogens only. This hypothesis is in agreement with the increasing evidence in periodontology supporting bacteria as the cause of the disease, but the individual's genetic makeup and environmental influences as determining the severity of the disease.^{64,68} Peri-implantitis can be considered multifactorial as well and includes host-related factors.^{64,65} Most likely, a complex interplay between the bacterial challenge and host factors determines whether a rapidly progressing peri-implantitis develops, leading to implant failure. Specific microorganisms may play a role in initiating this process but more likely are important in its maintenance or its progression.

CONCLUSION

In Table 4 the main conclusions derived from this comprehensive review of the literature are summarized, and references are provided that support these conclusions. Future research should concentrate on discovering relevant local and systemic conditions in the etiology of peri-implantitis. If these latter conditions are known, patients at risk can be defined and preoperative measures to increase implant survival can possibly be implemented. Probably this is a more rational approach than a microbial survey as such. Thus, a microbial survey can be reserved for patients who are potentially at risk, thus saving the costs and reducing the use of antibiotics in eradicating periopathogens.

REFERENCES

1. Brånemark P-I, Zarb GA, Albrektsson T (eds). Tissue-Integrated Prostheses: Osseointegration in Clinical Dentistry. Chicago: Quintessence, 1985.
2. Fiorellini JP, Martuscelli G, Weber HP. Longitudinal studies of implant systems. *Periodontol 2000* 1998;17:125–131.
3. Esposito M, Hirsch JM, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants. (I). Success criteria and epidemiology. *Eur J Oral Sci* 1998;106:527–551.
4. Mombelli A, Lang NP. The diagnosis and treatment of peri-implantitis. *Periodontol 2000* 1998;17:63–76.
5. Adell R, Lekholm U, Rockler B, Brånemark P-I. A 15-year study of osseointegrated implants in the treatment of the edentulous jaw. *Int J Oral Surg* 1981;10:387–416.
6. Tonetti MS, Schmid J. Pathogenesis of implant failures. *Periodontol 2000* 1994;4:127–138.
7. Esposito M, Hirsch JM, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants (II). Etiopathogenesis. *Eur J Oral Sci* 1998;106:721–764.
8. Socransky SS, Haffajee AD. Microbiology of periodontal disease. In: Lindhe J, Karring T, Lang NP (eds). *Clinical Periodontology and Implant Dentistry*, ed 3. Copenhagen: Munksgaard, 1997:138–188.
9. Slots J. Microflora in the healthy gingival sulcus in man. *Scand J Dent Res* 1977;85:247–254.
10. Tanner A, Maiden MF, Macuch PJ, Murray LL, Kent RL Jr. Microbiota of health, gingivitis, and initial periodontitis. *J Clin Periodontol* 1998;25:85–98.
11. Haffajee AD, Cugini MA, Tanner A, et al. Subgingival microbiota in healthy, well-maintained elder and periodontitis subjects. *J Clin Periodontol* 1998;25:346–353.
12. Ximenez-Fyvie LA, Haffajee AD, Socransky SS. Microbial composition of supra- and subgingival plaque in subjects with adult periodontitis. *J Clin Periodontol* 2000;27:69–75.
13. Riviere GR, Smith KS, Tzagaroulaki E, et al. Periodontal status and detection frequency of bacteria at sites of periodontal health and gingivitis. *J Periodontol* 1996;67:109–115.
14. Griffen AL, Becker MR, Lyons SR, Moeschberger ML, Leys KU. Prevalence of *Porphyromonas gingivalis* and periodontal health status. *J Clin Microbiol* 1998;36:3239–3242.

- COPYRIGHT © 2002 BY QUINTESSENCE PUBLISHING CO. INC. PRINTING OF THIS DOCUMENT IS RESTRICTED TO PERSONAL USE ONLY. NO PART OF THIS ARTICLE MAY BE REPRODUCED OR TRANSMITTED IN ANY FORM WITHOUT WRITTEN PERMISSION FROM THE PUBLISHER.
15. Haffajee AD, Socransky SS. Microbial etiological agents of destructive periodontal diseases. *Periodontol* 2000 1994; 5:78–111.
 16. Danser MM, van Winkelhoff AJ, de Graaff J, Loos BG, van der Velden U. Short-term effect of full-mouth extraction on periodontal pathogens colonizing the oral mucous membranes. *J Clin Periodontol* 1994;21:484–489.
 17. Socransky SS, Manganiello SD. The oral microbiota of man from birth to senility. *J Periodontol* 1971;42:485–496.
 18. Mombelli A, Lang NP. Microbial aspects of implant dentistry. *Periodontol* 2000 1994;4:74–80.
 19. Gusberti FA, Gada TG, Lang NP, Geering AH. Cultivable microflora of plaque from full denture bases and adjacent palatal mucosa. *J Biol Buccale* 1985;13:227–236.
 20. Nakou M, Mikx FHM, Oosterwaal PJM, Krijnen JCWM. Early microbial colonization of perimucosal implants in edentulous patients. *J Dent Res* 1987;66:1654–1657.
 21. Mombelli A, Buser D, Lang NP. Colonization of osseointegrated titanium implants in edentulous patients. Early results. *Oral Microbiol Immunol* 1988;3:113–120.
 22. Sordyl CM, Simons AM, Molinari JA. The microbial flora associated with stable endosseous implants. *J Oral Implantol* 1995;21:19–22.
 23. Danser MM, van Winkelhoff AJ, de Graaff J, van der Velden U. Putative periodontal pathogens colonizing oral mucous membranes in denture-wearing subjects with a past history of periodontitis. *J Clin Periodontol* 1995;22:854–859.
 24. Mombelli A, Mericske-Stern R. Microbiological features of stable osseointegrated implants used as abutments for overdentures. *Clin Oral Implants Res* 1990;1:1–7.
 25. Quirynen M, Listgarten MA. Distribution of bacterial morphotypes around natural teeth and titanium implants ad modum Branemark. *Clin Oral Implants Res* 1990;1:8–12.
 26. Dharmar S, Yoshida K, Adachi Y, Kishi M, Okuda K, Sekine H. Subgingival microbial flora associated with Brånemark implants. *Int J Oral Maxillofac Implants* 1994;9:314–318.
 27. Papaioannou W, Quirynen M, Nys M, van Steenberghe D. The effect of periodontal parameters on the subgingival microbiota around implants. *Clin Oral Implants Res* 1995;6:197–204.
 28. Quirynen M, Papaioannou W, van Steenberghe D. Intraoral transmission and the colonization of oral hard surfaces. *J Periodontol* 1996;67:986–993.
 29. Kohavi D, Greenberg R, Raviv E, Sela NL. Subgingival and supragingival microbial flora around healthy osseointegrated implants in partially edentulous patients. *Int J Oral Maxillofac Implants* 1994;9:673–678.
 30. Mombelli A, Marxer M, Gaberthuel T, Grunder U, Lang NP. The microbiota of osseointegrated implants in patients with a history of periodontal disease. *J Clin Periodontol* 1995;22:124–130.
 31. Papaioannou W, Quirynen M, van Steenberghe D. The influence of periodontitis on the subgingival flora around implants in partially edentulous patients. *Clin Oral Implants Res* 1996;7:405–409.
 32. Mengel R, Stelzel M, Hasse C, Flores-de-Jacoby L. Osseointegrated implants in patients treated for generalized severe adult periodontitis. An interim report. *J Periodontol* 1996;67:782–787.
 33. Kalykakis GK, Mojon PH, Nisengard R, Spiekermann H, Zafiroopoulos G-G. Clinical and microbial findings on osseointegrated implants: Comparisons between partially dentate and edentulous subjects. *Eur J Prosthodont Restorative Dent* 1998;6:155–159.
 34. Keller W, Brägger U, Mombelli A. Peri-implant microflora of implants with cemented and screw retained suprastructures. *Clin Oral Implants Res* 1998;9:209–217.
 35. Lee KH, Maiden MF, Tanner AC, Weber HP. Microbiota of successfully osseointegrated dental implants. *J Periodontol* 1991;70:131–138.
 36. Lee KH, Tanner AC, Maiden MF, Weber HP. Pre- and post-implantation microbiota of the tongue, teeth, and newly placed implants. *J Clin Periodontol* 1999;26:822–832.
 37. Sbordone L, Barone A, Ciaglia RN, Ramaglia L, Iacono VJ. Longitudinal study of dental implants in a periodontally compromised population. *J Periodontol* 1999;70:1322–1329.
 38. Hultin M, Gustafsson A, Klinge B. Long-term evaluation of osseointegrated dental implants in the treatment of partly edentulous patients. *J Clin Periodontol* 2000;27:128–133.
 39. Koka S, Razzoog ME, Bloem TJ, Syed S. Microbial colonization of dental implants in partially edentulous subjects. *J Prosthet Dent* 1993;70:141–144.
 40. Leonhardt A, Adolfsson B, Lekholm U, Wikstrom M, Dahlen G. A longitudinal microbiological study on osseointegrated titanium implants in partially edentulous patients. *Clin Oral Implants Res* 1993;4:113–120.
 41. Pontoriero R, Tonelli MP, Carnevale G, Mombelli A, Nyman SR, Lang NP. Experimentally induced peri-implant mucositis. A clinical study in humans. *Clin Oral Implants Res* 1994;5:254–259.
 42. Van Winkelhoff AJ, Goene R, Benschop C, Folmer T. Early colonization of dental implants by putative periodontal pathogens in partially edentulous patients. *Clin Oral Implants Res* 2000;11:511–520.
 43. Kalykakis G, Zafiroopoulos G-G, Murat Y, Spiekermann H, Nisengard RJ. Clinical and microbiological status of osseointegrated implants. *J Periodontol* 1994;65:766–770.
 44. Alcoforado GA, Rams TE, Feik D, Slots J. Microbial aspects of failing osseointegrated dental implants in humans. *J Periodontol* 1990;10:11–18.
 45. Rams TE, Roberts TW, Feik D, Molzan AK, Slots J. Clinical and microbiological findings on newly inserted hydroxyapatite-coated and pure titanium human dental implants. *Clin Oral Implants Res* 1991;2:121–127.
 46. Mombelli A, van Oosten M, Schurch E, Lang NP. The microbiota associated with successful or failing osseointegrated titanium implants. *Oral Microbiol Immunol* 1987; 2:145–151.
 47. Listgarten MA, Lai CH. Comparative microbiological characteristics of failing implants and periodontally diseased teeth. *J Periodontol* 1999;70:431–437.
 48. Malmstrom HS, Fritz ME, Timmis DP, Van Dyke T. Osseointegrated implant treatment of a patient with rapidly progressive periodontitis. A case report. *J Periodontol* 1990;61:300–304.
 49. Fardal O, Johannessen AC, Olsen I. Severe, rapid progressing peri-implantitis. *J Clin Periodontol* 1999;26:313–317.
 50. Nevins M, Langer B. The successful use of osseointegrated implants for the treatment of the recalcitrant periodontal patient. *J Periodontol* 1995;66:150–157.
 51. Rosenberg ES, Torosian JP, Slots J. Microbial differences in 2 clinically distinct types of failures of osseointegrated implants. *Clin Oral Implants Res* 1991;2:135–144.
 52. Savitt ED, Socransky SS. Distribution of certain subgingival microbial species in selected periodontal conditions. *J Periodontol Res* 1984;19:111–113.

53. Sanz M, Newman MG, Nachnani S, Holt R, Stewart R, Flemmig T. Characterization of the subgingival microbial flora around endosteal sapphire dental implants in partially edentulous patients. *Int J Oral Maxillofac Implants* 1990;5:247-253.
54. Lekholm U, Adell R, Lindhe J, et al. Marginal tissue reactions at osseointegrated titanium fixtures (II). A cross-sectional retrospective study. *Int J Oral Maxillofac Surg* 1986;15:53-61.
55. Palmisano DA, Mayo JA, Block MS, Lancaster DM. Subgingival bacteria associated with hydroxylapatite-coated dental implants: Morphotypes and trypsin-like enzyme activity. *Int J Oral Maxillofac Implants* 1991;6:313-318.
56. Tanner A, Maiden MF, Lee K, Shulman LB, Weber HP. Dental implant infections. *Clin Infect Dis* 1997;25(suppl 2):S213-S217.
57. Danser MM, van Winkelhoff AJ, van der Velden U. Periodontal bacteria colonizing oral mucous membranes in edentulous patients wearing dental implants. *J Periodontol* 1997;68:209-216.
58. Lekholm U, Ericsson I, Adell R, Slots J. The condition of the soft tissues at tooth and fixture abutments supporting fixed bridges. A microbiological and histological study. *J Clin Periodontol* 1986;13:558-562.
59. Adell R, Lekholm U, Rockler B, et al. Marginal tissue reactions at osseointegrated titanium fixtures (I). A 3-year longitudinal prospective study. *Int J Oral Maxillofac Surg* 1986;15:39-52.
60. Apse P, Ellen RP, Overall CM, Zarb GA. Microbiota and crevicular fluid collagenase activity in the osseointegrated dental implant sulcus: A comparison of sites in edentulous and partially edentulous patients. *J Periodontol* 1989;24:96-105.
61. Augthun M, Conrads G. Microbial findings of deep peri-implant bone defects. *Int J Oral Maxillofac Implants* 1997;12:106-112.
62. Salcetti JM, Moriarty JD, Cooper LF, et al. The clinical, microbial, and host response characteristics of the failing implant. *Int J Oral Maxillofac Implants* 1997;12:32-42.
63. Leonhardt A, Renvert S, Dahlen G. Microbial findings at failing implants. *Clin Oral Implants Res* 1999;10:339-345.
64. Wilson TG. Not all patients are the same: Systemic risk factors for adult periodontitis. *Gen Dent* 1999;47:580-588.
65. Wilson GW, Nunn M. The relationship between the interleukin-1 periodontal genotype and implant loss. Initial data. *J Periodontol* 1999;70:724-729.
66. Kronstrom M, Svensson B, Erickson E, Houston L, Braham P, Persson GR. Humoral immunity host factors in subjects with failing or successful titanium dental implants. *J Clin Periodontol* 2000;27:875-882.
67. Timmerman MF, van der Weijden GA, Abbas F, et al. Untreated periodontal disease in Indonesian adolescents. Subgingival microbiota in relation to experienced progression of periodontitis. *J Clin Periodontol* 2001;28:617-627.
68. McGuire MK, Nunn ME. Prognosis versus actual outcome IV. The effectiveness of clinical parameters and IL-1 genotype in accurately predicting prognoses and tooth survival. *J Periodontol* 1999;70:49-56.