Histopathologic Observations on Early Oral Implant Failures

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The purpose of this study was to morphologically describe the tissues surrounding 20 early failed (prior to prosthesis placement) Brånemark System oral implants. The implants and their surrounding tissues were consecutively retrieved and analyzed with light microscopy and transmission electron microscopy. Failures were chronologically divided into those occurring prior to, at, and after abutment connection. The clinical conditions varied from osteomyelitis to totally asymptomatic but mobile implants. Different histopathologic pictures were observed, ranging from a stratified, almost acellular, connective tissue layer, via a capsule with a great number of inflammatory cells, to a heterogeneous interface with areas of highly vascularized connective tissue and portions of poorly mineralized bone detached from the implant surface. The histopathologic variation may reflect different etiologies and/or time stages of the failure process. Epithelial downgrowth was occasionally observed for asymptomatic submerged implants. Epithelial cells were attached to the failed implant surface via hemidesmosomes. The histologic, clinical, and radiographic findings together indicated that 3 major etiologies might have been implicated in the failure processes: impaired healing ability of the host bone site, disruption of a weak bone-to-implant interface after abutment connection, and infection in situations with complicated surgery.
(Int J Oral Maxillofac Implants 1999;14:798–810)

Key words: dental implant, early failures, morphology, titanium, ultrastructure

Implants are commonly and successfully used as bone-anchoring elements in oral prosthetic rehabilitation. A firm and direct anchorage of the implant to surrounding bone, a condition defined as "osseointegration,"[1] is presumably the most important factor to explain the reported long-term clinical success of oral implants. Despite high success rates,[2–5] failures do occur. Therefore, to further optimize the outcome, etiologies and factors associated with implant failure should be elucidated. Conceivably, such knowledge is needed for developing adequate treatment and prevention strategies.

The epidemiology and factors associated with oral implant failures have recently been reviewed.[6,7] Implant losses can arbitrarily be divided into early (failure to achieve osseointegration) and late (failure to maintain the established osseointegration) losses.[6] One way to discriminate between early and late losses is to include all failures occurring before prosthesis placement in the early group and those occurring after functional loading in the late group, if implants are not immediately loaded. Obviously, this subdivision has limitations, as do all classifications, since it remains difficult to clinically determine to what extent an implant is actually osseointegrated. Limitations of this classification may be particularly evident for implants that are found to be clinically stable at abutment connection, but which become mobile before placement of the definitive prosthesis.[8]

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It is believed that excessive surgical trauma, impaired healing, bacterial contamination, and premature overloading may be the most common causes of implant failure at an early stage after implant placement. Excessive occlusal stress in conjunction with host characteristics and bacterial-induced marginal bone loss (peri-implantitis) seem to be the major etiologic factors for late losses (apart from mechanical breakdown).[7]

The first histologic description of early implant failure was provided by Brånemark et al[9] in animals 3 decades ago. This investigation was followed by a detailed ultrastructural description of tissues surrounding early failures of 1-stage blade implants, both in monkeys and humans.[10] Unfortunately, no description of the clinical picture was given. Thereafter, only sporadic studies, mainly in the form of single case reports, have been published regarding this matter.[11–18] In 2 recent articles,[17,18] early failures were attributed to overheating of the surgical site. However, since the authors stated that bacteria were observed in all their specimens, infection could have been an alternative cause. As judged by the scientific literature, no firm evidence of the mechanisms for early failures has been reported. However, the epidemiology of early losses has been described in relation to different implant systems, anatomic locations, and other factors.[6,8,19–23]

Once implant failures are recognized as being disease-related, a comprehensive view of the problem, as with any other medical condition, might be obtained. Therefore, it is useful to analyze the epidemiology (prevalence of the disease and various interrelated factors), the histopathology (the gross and microscopic changes of the disease), the pathogenesis (the disease history), and the pathophysiology (the mechanisms of the disease) of implant losses and complications.

The objective of the present study was to analyze the histomorphology of tissues surrounding early failures of oral implants in relation to the clinical history and radiographic findings so as to acquire additional information about possible failure mechanisms.

Materials and Methods

Clinical Data. Twenty failed, commercially pure titanium implants (Brånemark System, Nobel Biocare AB, Göteborg, Sweden), consecutively removed before prosthesis placement (early losses) from 17 patients (11 females and 6 males) treated at the Brånemark Clinic, Göteborg University, Göteborg, Sweden, were included in this study (Table 1). One implant was removed 3 weeks after loading and it may be argued that it should be considered as a late loss. However, radiographic signs of failure were evident 2 months after placement (Fig 1).

The following information was recorded at retrieval: additional postoperative drugs (type, dosage, and duration) and diseases; symptoms and their duration; peri-mucosal conditions (visual signs); manual implant stability assessment; and any relevant additional finding. The remaining information presented in Table 1 was obtained retrospectively by searching the patient's history and included the following: medical and oral anamnesis including smoking habits; implant operation notes (jaw bone resorption anatomy and bone quality at the implant site,[24] vascularization, preparation of the implant site, primary implant stability, and number, length, and type of implants placed); pre- and post-medication; and any additional relevant information.

Failed implants had various lengths (from 6 to 18 mm; 5 implants ≤ 8 mm) as well as diameters (from 3.75 to 5 mm; 2 were 5 mm wide and 3 were 4 mm wide) and were placed in different arch shapes and bone qualities (6 in extremely resorbed jaws [Type D and E] and 3 implants in soft bone [Type 4]).[24] The majority of losses (14) occurred in totally edentulous patients and in maxillae (14). Four of the retrieved implants were placed in grafted bone of 3 patients (patients B, D, and K; Table 1).

All implants had been placed following a 2-stage surgical technique.[25] About 1 hour before implant surgery, patients had routinely been administered 2 g of phenoxymethylpenicillin (Kåvepenin, Astra Läkemedel AB, Södertälje, Sweden) orally. Postoperatively, the same antibiotic treatment was continued for 10 days (2 g + 2 g daily). In patients with penicillin allergy, 1 g erythromycin was administered at that time (Ery-Max, Astra Läkemedel AB, Södertälje, Sweden, or Abboticin, Abbot Skandinavia AB, Kista, Sweden), 1 hour preoperatively, and 1 g + 1 g daily for 10 days. However, patient G, allergic to penicillin, specifically asked for Vibramycin, which was not available at the clinic. Patient N, also allergic to penicillin, was operated on under total anesthesia and received 0.2 g of tetracycline intravenously, 1½ hours after induction of the general anesthesia. Both patients G and N received postoperatively 100 mg of tetracycline (Vibramycin, Pfizer AB, Täby, Sweden) twice a day for 10 days. Therefore, no preoperative antibiotics were administered to those patients.

All implants were checked for stability by manual manipulation and/or rotation of each implant with a pair of forceps or a screwdriver, respec-

Table 1 Clinical Data of Patients with Failed Implants

Patient	Age*/ sex	Smoker?	Implant length/ diameter	Implant position†	Primary stability	Jaw shape/ bone quality‡	Total no. of implants	Time of retrieval	Implant mobility and symptoms	Additional surgical notes	Radiographic findings
A	62/F	Yes	1. 6 mm/5 mm	R3 maxilla	Bad	C/4 (P)	3	Abutment connection	Mobility, no symptoms	—	Not performed
B	52/M	No	2. 13 mm/3.75 mm	R3 maxilla	Optimal	E/3 (T)	5	Abutment connection	Mobility, no symptoms	Onlay bone grafting	Not performed
C	75/M	No	3. 10 mm/3.75 mm	R3 mandible	Optimal	B/2 (P)	6	Abutment connection	Mobility, no symptoms	—	Not performed
D	35/M	Yes	4. 15 mm/3.75 mm	R3 maxilla	Good	E/2 (T)	6	Abutment connection	Mobility, no symptoms	Onlay bone grafting	Not performed
E	65/F	No	5. 7 mm/3.75 mm	R3 mandible	Optimal	E/3 (T)	6	Abutment connection	Mobility, no symptoms	—	Not performed
F	79/F	No	6. 13 mm/3.75 mm	R3 maxilla	Good	C/4 (T)	7	5 weeks after abutment connection	Mobility, no symptoms	—	None 5 weeks before removal
G	54/F	Yes	7. 18 mm/3.75 mm	L2 mandible	Optimal	C/2 (P)	3	9 weeks after implant placement	No mobility, swelling, pain, fistula, pus	Complicated nerve transposition	Peri-apical bone rarefaction
			8. 18 mm/3.75 mm	L3 mandible	Optimal	C/2 (P)		10 weeks after implant placement	No mobility, swelling, pain, fistula, pus	Complicated nerve transposition	Peri-apical bone rarefaction
H	66/F	Yes	9. 13 mm/3.75 mm	R1 maxilla	Optimal	C/3 (T)	6	4 weeks after implant placement	Mobility, barrier exposure, pus	Barrier augmentation	Not performed
I	74/F	No	10. 13 mm/4 mm	L1 maxilla	Optimal	B/4 (T)	6	Abutment connection	Mobility, no symptoms	—	Not performed
J	36/F	Yes	11. 10 mm/3.75 mm	R1 mandible	Optimal	B/2 (P)	4	Abutment connection	Mobility, no symptoms	—	Not performed
K	59/F	Yes	12. 10 mm/3.75 mm	R1 maxilla	Bad	D/3 (T)	6	3 weeks after abutment connection	Mobility, pain at percussion	Onlay bone grafting	None 3 weeks before removal
			13. 7 mm/3.75 mm	L1 maxilla	Bad	D/3 (T)		3 weeks after abutment connection	Mobility, pain at percussion	Onlay bone grafting	None 3 weeks before removal
L	72/M	No	14. 7 mm/4 mm	L3 maxilla	Good	C/4 (T)	6	Abutment connection	Mobility, no symptoms	—	Not performed
M	56/F	No	15. 8 mm/5 mm	R4 maxilla	Good	D/2 (T)	6	2 weeks after abutment connection	Mobility, pain at percussion	—	Not performed
N	50/F	Yes	16. 10 mm/4 mm	L3 mandible	Optimal	B/4 (P)	6	After 3 weeks of loading	No mobility, fistula, pus	Complicated operation	Radiolucency with irregular contours
O	52/F	Yes	17. 15 mm/3.75 mm	L1 maxilla	Optimal	C/3 (T)	6	3 months after abutment connection	Mobility, no symptoms	—	None 3 months before removal
P	63/M	Yes	18. 13 mm/3.75 mm	R3 maxilla	Optimal	B/3 (T)	7	2 weeks after abutment connection	Mobility, pain at percussion	—	Not performed
			19. 13 mm/3.75 mm	L1 maxilla	Optimal	B/3 (T)		2 weeks after abutment connection	Mobility, pain at percussion	—	Not performed
Q	53/M	Yes	20. 10 mm/3.75 mm	R3 maxilla	Optimal	B/3 (T)	6	Abutment connection	Mobility, no symptoms	—	Not performed

*Age at implant placement.
†R = right, L = left, 1,2,3, respectively = mesial, medial, and distal implant.
‡Jaw shape and bone quality according to Lekholm and Zarb.[24] T = totally edentulous; P = partially edentulous.
Patient B: 3 of the 4 remaining implants failed after 3 months of loading.
Patient F: Implant was found to be mobile 2 weeks after abutment connection.
Patient G: No preoperative antibiotics. Complicated nerve transposition resulting in osteomyelitis and hyperesthesia.
Patient H: 2 nonresorbable barriers for bone augmentation were used. Also, implant L3 was removed due to infection (barrier exposure, swelling, large buccal bone defect, and implant mobility) 5 months after implant placement.
Patient K: Implant L3 was also removed at abutment connection.
Patient M: 5 of 6 implants placed previously failed; R1 was removed at abutment connection.
Patient N: No preoperative antibiotics. Complicated operation in total anesthesia: a life-threatening hemorrhage occurred at the lingual right side and it took several hours of intervention to stop the bleeding. L2 was also removed (fistula, pus, and tenderness) 3 months after placement (Fig 1).
Patient O: The implant was found to be mobile 2 months after abutment connection, but was removed 1 month later in general anesthesia.

tively, at abutment connection and at each visit before prosthesis placement. If mobility was found, the implant was removed.

The reason for implant removal was, in all cases, a clinically observed failure, which included either of the following 2 major situations:

1. A manifest infection in the surrounding tissues, characterized by signs such as swelling, pain, fistula, presence of purulent exudate (4 implants in patients G, H, and N; Table 1), often in the absence of clinically detectable implant mobility (3 implants in patients G and N). These implants were removed either before (patients G and H) or after abutment connection (patient N).
2. Presence of mobility (16 implants) either in the way of (a) mobility recorded at abutment connection and in the absence of other pathologic signs (9 implants in patients A, B, C, D, E, I, J, L, and Q), or (b) mobility recorded by the prosthodontist during the prosthetic procedures (7 implants in patients F, K, M, O, and P). Often, but not always, mobility was found in conjunction with a painful sensation when trying to rotate the implant.

At the time of retrieval, the submerged implants were exposed via a flap procedure, after local anesthesia with 2% Lidocaine/Epinephrine (Astra Läkemedel AB). Sixteen implants were gently unscrewed with the aim of maintaining as much of the peri-implant tissues as possible attached to the implant. To preserve the implant/tissue interface in a better way, 4 implants (patients F, O, and P) were retrieved using a trephine bur (5 mm in diameter) at a maximum speed of 2000 rpm, under generous saline cooling. Informed consent was obtained from all patients. After removal of the

Figs 1a to 1c Sequence of intraoral radiographs showing the development of peri-implant lesions in patient N. Two months after implant surgery, a fistula originating from the middle implant was evident and the area was tender. At exploratory surgery the implant was found to be stable. (a) A distinct periapical radiolucency with irregular borders was observed 1 week later around the middle implant, which was removed (implant not analyzed in the present investigation, but still stable at retrieval). Also the distal implant was surrounded by a less distinct radiolucent line. (b) At abutment connection, the distal implant was stable despite the diffuse radiolucency. (c) At final prosthesis placement, the distal implant was stable even though surrounded by a diffuse peri-implant radiolucency. One week later a fistula with purulent exudate originating from the apical portion of the implant was observed. The implant was still stable, although it was easily removed.

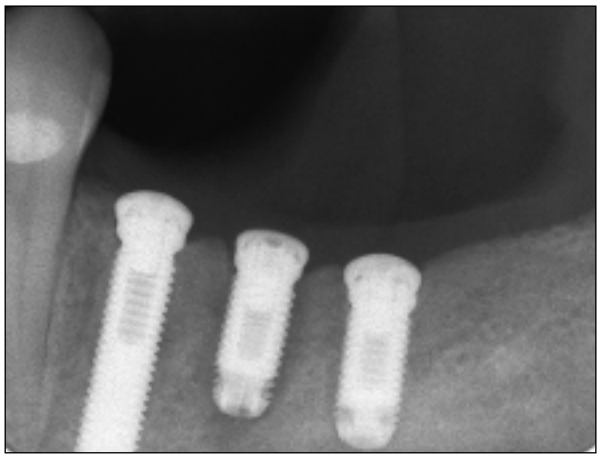


Fig 1a

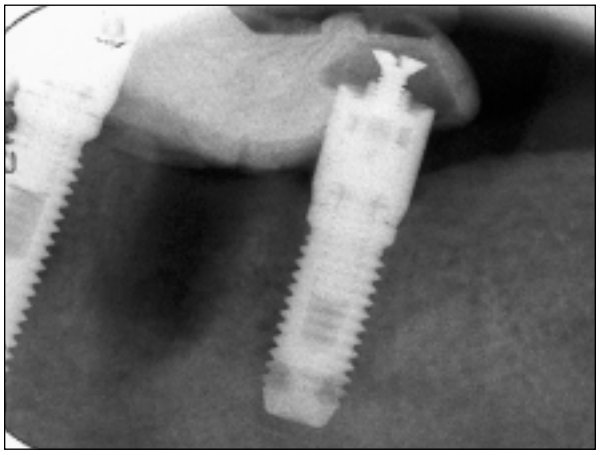


Fig 1b

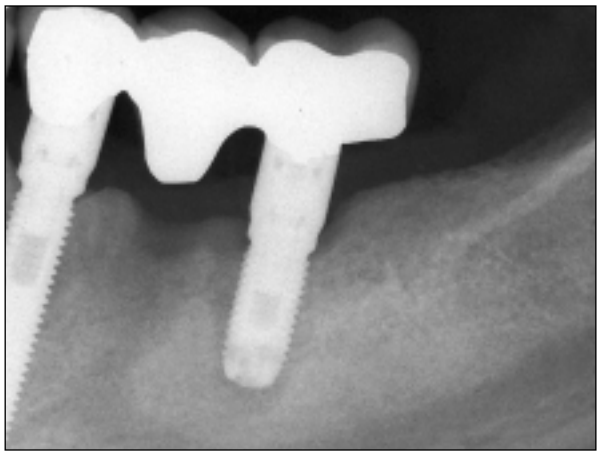


Fig 1c

failed implants, the sites were carefully curetted and closed via a flap procedure. All implant sites, with the exception of those of patient G, healed uneventfully. In patient G, the implant sites were affected by osteomyelitis, a condition that required several months of antibiotic treatment and surgical debridement to heal completely.

The retrieved implants were chronologically divided into 3 groups: implants that failed before abutment connection (group 1 including 3 implants), failures identified at abutment connection (group 2 including 9 implants), and losses that occurred after abutment connection, but before the definitive placement of the prosthesis (group 3 including 8 implants).

As a rule, no radiographs were taken of implants removed up to the time of abutment connection, unless the surgeon, in the presence of clinical signs and symptoms, decided otherwise (patients G and N). Intraoral radiographs were routinely taken at abutment connection to verify proper abutment seating. Obtained radiographs were also inspected with regard to density and architecture of the bone around the implant.

Tissue Sample Preparation. Sixteen of the retrieved implants, together with their surrounding tissues, were immediately immersed in a 2.5% glutaraldehyde in 0.01 mol/L sodium cacodylate fixative solution (pH 7.4). Three other implants (patients A, C, and D) were fixed in a 4% buffered formalin solution (pH 7.4), whereas 1 specimen (patient Q) was immediately frozen and processed for immunohistochemistry, as previously described.[26] The specimens were kept in a fixative solution for between 48 hours and 2 weeks before being postfixed for 1 hour in 2% osmium tetroxide, dehydrated in increasing concentrations of ethanol to absolute ethanol, and, finally, embedded in plastic resin (LR White, The London Resin Co Ltd, Hampshire, England).

The embedded specimens were divided longitudinally into 2 parts by sawing. One half was subsequently cut horizontally in 2 and 3 pieces, depending on the implant length, and processed with an electropolishing technique[27] to obtain sections with an intact implant-tissue interface for light microscopy (LM) and transmission electron microscopy (TEM). In brief, by an electrochemical procedure the bulk part of the implant was dissolved, while a thin intact oxide layer was left in direct contact with the tissue. The specimens were mounted in a sample holder and immersed in an electrolyte containing 5% perchloric acid, 60% methanol, and 35% n-buthanol and cooled to –30˚C. The specimen served as an anode and was surrounded by a platinum cathode. The electropolishing was performed at 24 V for 2 to 4 hours. Afterward, the specimens were carefully rinsed in tap water and reembedded in plastic resin (Agar 100, Agar Aids, Stansted, Essex, England).

Longitudinal thin sections (1 µm) were cut for LM using a microtome (Microm HM 350, Carl Zeiss AB, Stockholm, Sweden) with glass knives and stained with 1% Azur II and 1% methylene blue in 1% disodium tetraborate. Selected areas were cut for TEM using an ultramicrotome (Ultracut, Reichert-Jung, Vienna, Austria) with diamond knives and contrasted with uranyl acetate and lead citrate. The remaining half of selected implant-containing specimens were ground sectioned (down to 10 to 20 µm thickness)[28] and stained with 1% toluidine blue or subjected to the fracture technique,[29] sectioned, and stained as the electropolished specimens.

Sections for LM were examined and photographed in a Nikon Microphot FXA microscope (Bergström Instrument AB, Göteborg, Sweden). Histometric data were obtained using Leitz Microvid equipment mounted to a Leitz Metallux 3 microscope (Leica Microsystems AB, Sollentuna, Sweden) connected to a personal computer. Transmission electron microscopy was performed in a Zeiss CEM 902 (Carl Zeiss AB) on sections 70 to 80 nm thick.

Results

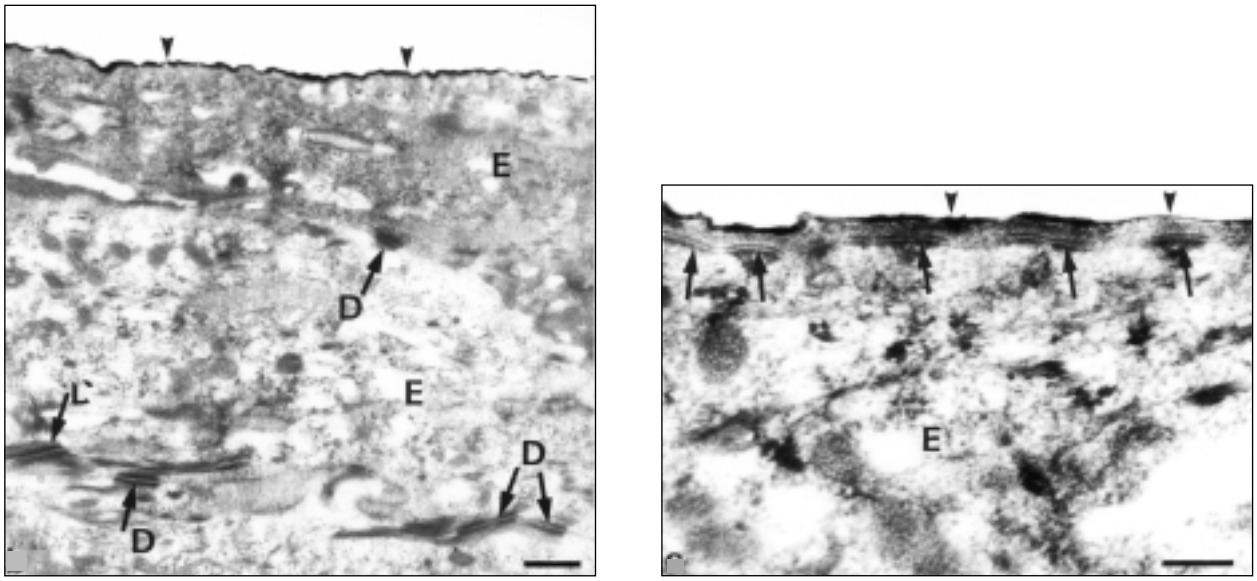
Clinical and Radiographic Observations. A detailed description of the clinical data of patients with failed implants is presented in Table 1. From intraoral radiographs taken either to investigate the origin of some clinical symptoms (3 implants in patients G and N) or to ascertain whether the abutment was properly seated (4 implants in patients F, K, O), 2 distinctly different radiographic pictures emerged. Where symptoms of infection presented (patients G and N), a diffuse radiolucency with irregular borders surrounding a large portion of the implant was present (Fig 1). In contrast, implants that were asymptomatic and clinically stable at abutment connection, but which were loose a few weeks later, before prosthesis placement, seemed to have normal bone tissue in close contact with the implant surface. An exception was the implant from patient O, in which a very thin, radiolucent peri-implant space seemed to surround the entire implant at abutment connection. However, this observation was made retrospectively.

Histopathologic Observations (LM and TEM). For 6 implants, inadequate amounts of tissues

Table 2 Histopathologic Observations of Tissues Surrounding Failed Implants in Relation to the Chronologic Sequence of Failure and Clinical Symptomatology

Implant no. (patient)	Failure time	Symptomatology	Additional notes	Main histologic findings at the interface
7 (G)	Before abutment connection	Swelling, pain, fistula, and pus	Complicated surgery/ osteomyelitis	Too little tissue
8 (G)	Before abutment connection	Swelling, pain, fistula, and pus	Complicated surgery/ osteomyelitis	Too little tissue
9 (H)	Before abutment connection	Wound dehiscence and pus	Barrier augmentation	Stratified connective tissue/ bone fragments in apical hole (TEM)
1 (A)	Abutment connection	None	Poor bone quality/quantity	Stratified connective tissue (TEM)
4 (D)	Abutment connection	None	Onlay bone grafting	Stratified connective tissue
2 (B)	Abutment connection	None	Onlay bone grafting	Stratified connective tissue/ bone fragments in apical hole (TEM)
10 (I)	Abutment connection	None	Poor bone quality	Too little tissue
14 (L)	Abutment connection	None	Poor bone quality/quantity	Too little tissue
5 (E)	Abutment connection	None	Poor bone quantity	Epithelial proliferation (TEM)
3 (C)	Abutment connection	None		Intense inflammatory cell infiltration, epithelial proliferation?
11 (J)	Abutment connection	None		Epithelial proliferation, intense imflammatory cell infiltration (TEM)
20 (Q)	Abutment connection	None		Intense inflammatory cell infiltration with plasma cells prevailing
17 (O)	After abutment connection	None		Stratified connective tissue
6 (F)	After abutment connection	None	Poor bone quality	Stratified connective tissue, chronic inflammation (TEM)
13 (K)	After abutment connection	Pain at percussion	Onlay bone grafting	Stratified connective tissue
12 (K)	After abutment connection	Pain at percussion	Onlay bone grafting	Too little tissue
15 (M)	After abutment connection	Pain at percussion	Poor bone quantity	Too little tissue
18 (P)	After abutment connection	Pain at percussion		Cellular fibrous tissue, non-mineralized bone separated from the interface (TEM)
19 (P)	After abutment connection	Pain at percussion		Non-mineralized bone as in #18 (P) (TEM)
16 (N)	After abutment connection	Fistula, pus	Complicated surgery	Intense inflammatory cell infiltration, epithelial proliferation (TEM)

attached to the implant were retrieved to permit histologic description (Table 2). In general, the preservation of tissues was adequate, albeit not optimal. For specimens in which the bulk of the implant was removed electrochemically, the implant surface was marked by a thin, dense electron line representing the surface oxide layer (Figs 2 and 3), sometimes with attached incompletely removed bulk material. In general, it was apparent that tissues had remained in contact with the implant surface. However, in many instances, exudates or spaces devoid of organized tissue were visible within some of the implant threads. A common feature observed in several specimens was the presence of erythrocytes between the tissue and the implant. This was also the case for implants retrieved with a trephine bur. It is very likely that these features represented artifacts, probably induced by the mechanical disruption of the interface at retrieval. Bacteria were not observed at the implant surface or in the surrounding tissues of any specimen.



Figs 2a and 2b Electron micrographs of tissues surrounding failed oral implant E5. (*Left*) The implant surface is represented by a dense line (*arrowheads*) remaining after the electrochemical removal of the bulk titanium. Epithelial cells (E) were in contact with the implant surface (fifth thread). Desmosomes (D) connected the epithelial cells. Bar = 0.5 µm. (*Right*) Implant surface is marked by arrowheads. Epithelial cell (E) was in contact with the implant. Numerous hemidesmosomes (*arrows*) were present in the plasma membrane facing the implant. Bar = 0.25 µm.

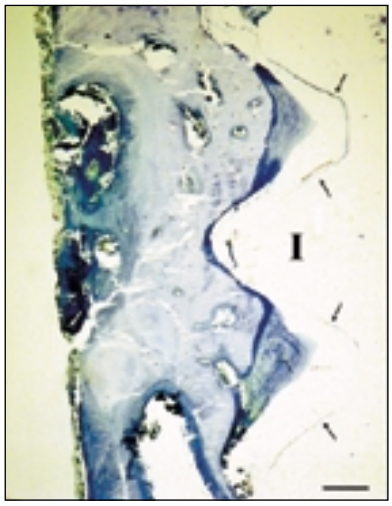


Fig 3 Photomicrograph of the tissues located at the middle portion of implant P18, removed 2 weeks after abutment connection because of mobility. A painful sensation was present when tapping or rotating the implant. Observe the separation of the mixed tissues (stratified connective tissue and poorly mineralized bone) from the electrolytically dissolved implant (I) (arrows denote the remaining titanium oxide layer). The presence of non-mineralized bone at the interface was confirmed by TEM (see Fig 7). Bar = 100 µm; Azur II and methylene blue stain.

The major histologic findings in relation to the chronologic sequence of implant losses are summarized in Table 2. Regarding group 1, retrieved before abutment connection and in which clinical signs and symptoms of infection were present at retrieval, a sufficient amount of tissue was found only in the bottom hole of 1 implant (patient H). In this specimen the tissue consisted of well-vascularized connective tissue containing few inflammatory cells. Fragments of bone tissue, not displaying signs of resorption, were embedded in stratified connective tissue (Fig 4). The identity of bone was confirmed by TEM.

In group 2, retrieved at abutment connection and where no clinical symptoms were apparent, bone was not found in direct contact with the implant surface in any specimen. However, different histologic patterns were found in the retrieved tissues. The first pattern (patients A, B, and D) was typical for a dense connective tissue capsule, with layers of collagen and flattened fibroblasts (Fig 5). Apart from inactive (as judged from their ultrastructure) macrophages, inflammatory cells were not present. In the bottom hole of implant B2, bone fragments were embedded in connective tissue, similar to that described above for specimen H.

A second histologic pattern was the presence of epithelial cells in contact with the implant surface. This was verified by TEM in specimens from

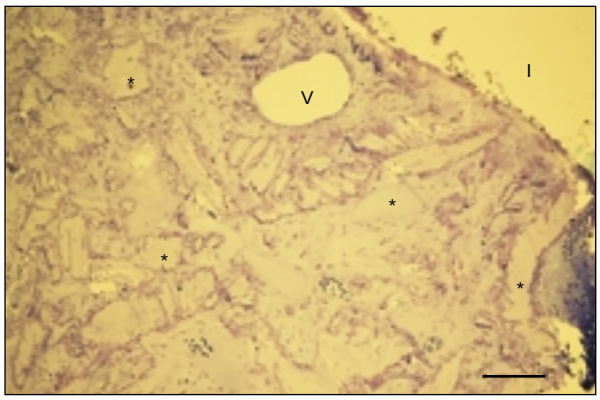


Fig 4 Photomicrograph of the tissue located in the apical hole of implant H9. I = implant (electrolytically dissolved). Large bone fragments (some of which are indicated by asterisks) were embedded in stratified connective tissue. The presence of bone was confirmed by TEM. No sign of bone resorption was evident. A large blood vessel (V) was present. No particular inflammatory reaction could be observed in this location. The implant was removed 4 weeks after placement because of barrier exposure and purulent exudate. At exploratory surgery it was found to be mobile and therefore removed. Bar = 100 µm; Azur II and methylene blue stain.

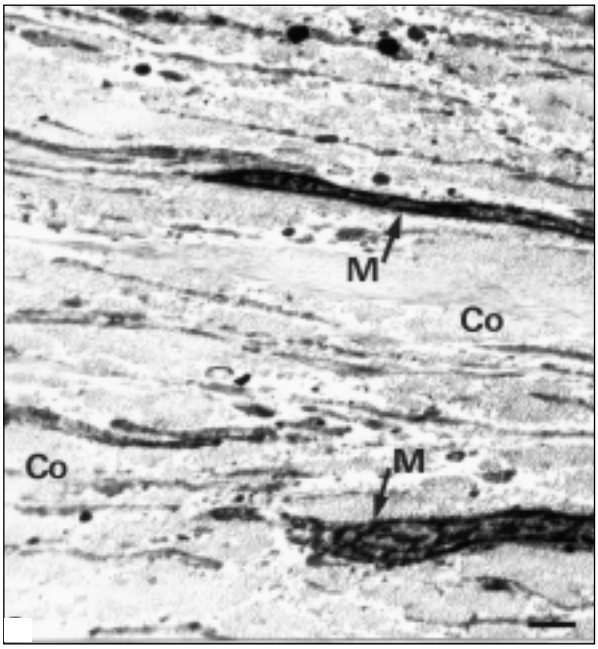
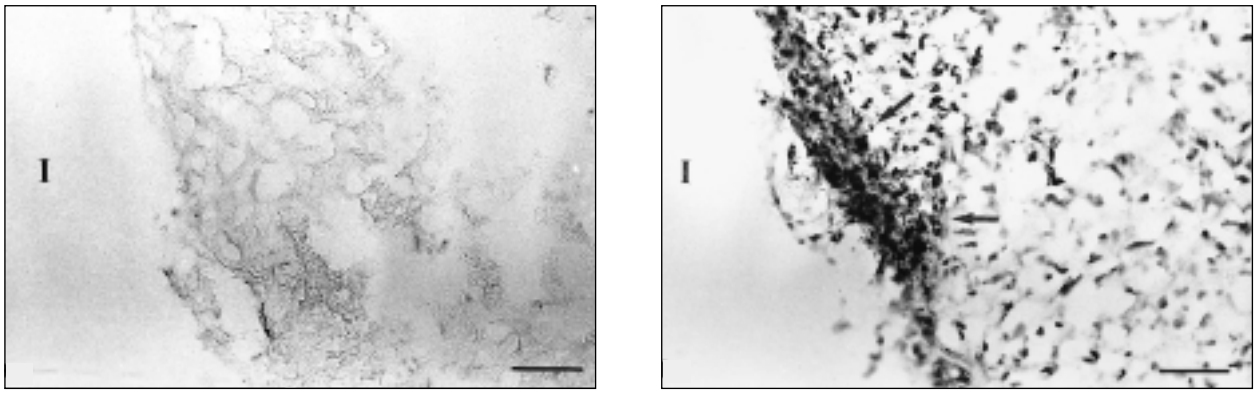


Fig 5 Electron micrograph of tissues surrounding implant A1. Formalin fixation. This implant was surrounded by a capsule consisting of stratified connective tissue. The major components were collagen bundles (Co) separating elongated profiles of fibroblasts and macrophages (M). Bar = 1 µm.

patients E (Fig 2) and J. Epithelial cells were probably also present in the specimen from patient C, although the exact location with respect to the implant surface was difficult to judge because of the detachment of the tissue from the implant at retrieval. The non-keratinized epithelial cells formed multiple layers and were connected to each other by desmosomes (Fig 2a). The epithelial cells were separated from the implant surface by a basal lamina about 500 nm wide. Numerous hemidesmosomes were present in the plasma membrane facing the implant surface (Fig 2b). In specimen J, polymorphonuclear leukocytes (PMNs), macrophages, and mutinucleated giant cells were also present in the implant-close zone of threads not containing epithelial cells.

The specimen from patient Q was examined by immunohistochemistry. Plasma cells were predominant and accumulated toward the implant surface (Fig 6). Other inflammatory cells such as macrophages, helper/inducer ($CD4^+$), and cytotoxic/suppresser ($CD8^+$) T-lymphocytes and B-cells were also present.

In group 3, retrieved after abutment connection but before prosthesis placement, the type of tissue around implants varied. In specimens from patients F, K, and O, stratified connective tissue was present close to the implant. The specimen from patient F, in addition, had threads containing inflammatory cells (macrophages and mutinucleated giant cells). In the 2 specimens from patient P, the tissue was detached from the implant surface (Fig 3). This separation may have occurred before or at the time of retrieval. Mineralized bone was present in both specimens, but was separated from the border at the tissue facing the implant by either a 100- to 300-µm-wide zone of stratified connective tissue or by a narrow, 7- to 8-µm-wide zone of nonmineralized bone (Fig 7). In patient N signs of infection (fistula and purulent exudate) were present at retrieval, and the tissue contained numerous plasma cells and PMNs. Cords, separated by soft connective tissue, containing loosely packed epithelial cells were also present, but the exact relationship to the surface could not be established, as the tissue was partially detached from the implant.



Figs 6a and 6b Photomicrographs of consecutive sections of the soft tissue present at the interface of implant Q20, retrieved at abutment connection. This specimen was evaluated by means of immunohistochemistry. I = implant (removed). (*Left*) Control section (omission of primary antibodies). (*Right*) Plasma cells (RFD6). Arrows point to accumulation of plasma cells at the interface. Interestingly, no clinical signs of infection were manifest. Bar = 50 µm; diaminobenzidine tetrahydrochloride (DAB) stain.

Discussion

In the present study, the morphology of tissues surrounding 20 failed Brånemark System implants was analyzed by means of LM and TEM.

Clinical Findings. In the present material 2 clinical situations were observed: mobility recorded at abutment connection, indicating that osseointegration had probably never been established (9 implants), and mobility, often in conjunction with a painful sensation, recorded by the prosthodontist when tightening the abutment screw (7 implants). It could be hypothesized that the degree of osseointegration achieved by the latter implants was unable to withstand either the stresses induced by the prosthetic procedures or the loading forces possibly generated by an unfavorable occlusion. As an alternative, the surgeon may have misjudged the primary implant stability condition.

A painful sensation elicited when tightening the abutment is generally associated clinically with implant mobility.[6] Despite its common use, this parameter has not been scientifically evaluated. It remains unclear whether a painful sensation could have been present for implants removed at abutment connection because of the effect of local anesthetic infiltration. The present observations indicate that pain may be associated with the process of implant failure, ie, disintegration of a weak bone-implant interface, which will be or has been replaced by a soft tissue interface. Such a process may have similarities with the fibrous healing of improperly stabilized bone fractures. However, not all implants in the present investigation seemed to involve a painful sensation.

Four implants (patients G, H, and N) showed swelling, fistulation, and purulent exudation. This symptomatology could have been related to infection of part of the implant site. In addition, the implant surgery was particularly traumatic in patients G and N, who did not receive preoperative antibiotics. Further, patient H was treated with nonresorbable barriers for bone augmentation. It is known that biomaterial-centered infections generally pursue an indolent course, with a characteristic reduced responsiveness to antibiotics.[30,31] Further, it is known that patients with higher plaque scores,[32] and with implants associated with infection signs,[33,34] are affected by higher early failure rates. An infection can also be transmitted to an implant from an adjacent infected tooth.[35] The observation that 3 of the 4 infected implants in the present study were removed from the 2 patients (G and N) who did not receive routine preoperative antibiotic prophylaxis, seems to be in agreement with the findings of Dent et al.[21] As it has been demonstrated that preoperative antibiotic administration significantly decreased the incidence of early failures,[21] the current results emphasize the importance of preoperative antibiotic coverage.

The radiographic examination provided valuable information, although in some situations the observations were in apparent contradiction with mobility assessment. For instance, 3 implants (patients G and N) with clinically manifest infection and displaying an evident radiolucency were not found to be mobile at repeated clinical inspections. The possibility that both surgeon and prosthodontist could have misjudged the implant stability testing is remote, since both were aware

of the clinical and radiographic pictures. Manual testing has been shown to be a reliable parameter for assessing implant stability, and the use of Periotest did not offer significant advantages.[36] This may indicate that part of the implant was still integrated in bone.

Radiographs obtained after abutment connection (patients F, K, and O) were unable to disclose with any degree of certainty the implants that were going to become mobile a few weeks later. A hypothesis is that weak integration or an insufficiently large area of bone-implant interface may have been damaged, either by prosthetic manipulation or by occlusal overloading, resulting in the formation of a soft tissue interface.

Methodologic Aspects. Only 4 implants were removed en bloc with a trephine bur (patients F, O, and P), while all the others lost part of the interface tissue during the retrieval procedures as a result of the attempts of the surgeon to be as conservative as possible and not create large bone defects by removing too much tissue. In all cases, implants retrieved with the trephine bur had enough attached tissue to allow adequate observations, whereas the tissue surrounding 6 of 16 implants that had been removed without a trephine bur was inadequate for histologic analysis (Table 2). Three other implants (patients C, J, and N) had their surrounding soft tissue capsule completely or partially detached from the surface at removal. The observation of erythrocytes in the threads of several implants, also when a trephine bur was used, indicates that the implant-tissue interface was broken and that bleeding occurred at the interface during implant retrieval. However, for the implants removed after abutment connection, the mobility testing procedure may also have caused bleeding because of mechanical disruption of the interface, as occasionally observed by Aspenberg and Herbertsson.[37]

Previous investigations have shown the suitability of the electropolishing technique for studies on metal-soft tissue interfaces. No alterations of the soft tissue morphology, induced by electropolishing, have been observed[27,38] (Källtorp et al, unpublished data). In some specimens, a fracture technique was used to separate tissues from implants.[29] However, in the present samples, dominated by soft tissue at the interface, portions of tissues were left on the implant surface. Ground sections[28] were more difficult to evaluate than electropolished sections, since they were up to 20 times thicker. Therefore, the electropolishing technique was found to be the best procedure available for a light microscopic and ultrastructural analysis of an intact interfacial zone. Nevertheless, because of the larger sizes and geometric complexities of clinical implants (internal threads, cover or abutment screws) as compared to experimental implants, the processing of clinical implants was technically highly demanding. The electropolishing technique, however, has been found to induce artifacts in the bone-implant interface in the form of demineralization and impregnation of titanium ions.[39] Therefore, it cannot be excluded that the bone demineralization observed in specimens P18 (Fig 7) and P19 could be artifactual.

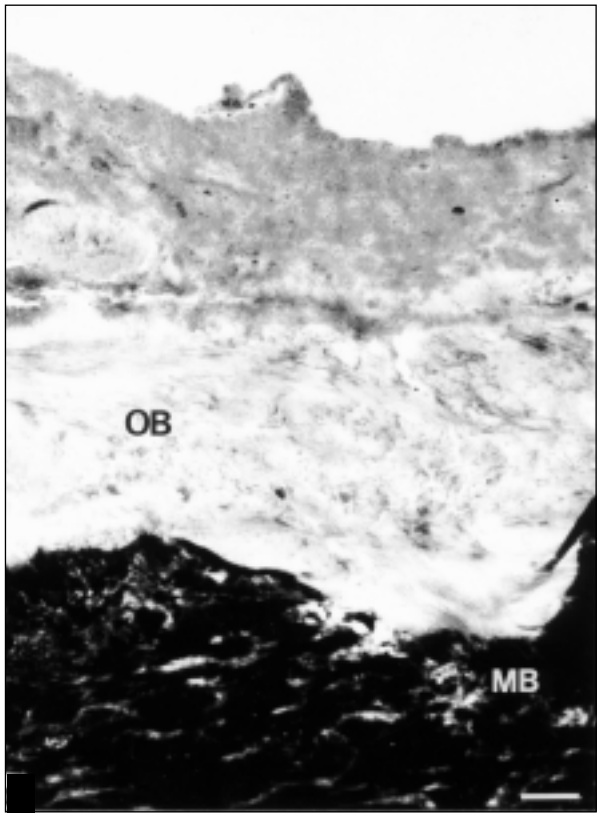


Fig 7 Electron micrograph of implant P18. In this specimen the tissue was separated from the implant by erythrocytes indicating bleeding before or at retrieval. Mineralized bone (MB) and, closer to the implant, a 7- to 8-µm-wide zone of non-mineralized bone (OB) was present. Bar = 1 µm.

Histopathologic Findings. The morphologic examination of tissues around failed, asymptomatic implants removed at abutment connection revealed a lack of osseointegration and formation of a fibrous capsule. In particular, bone was absent from all the threads of clinically mobile implants. Two different histologic pictures were observed, which may represent different stages of the failure process. Some implants (patients A, B, and D) were surrounded by a dense connective tissue capsule rich in fibroblasts and collagen bundles

aligned parallel to the implant surface, but with few inflammatory cells. Such a picture shows consistent histologic similarities to implants placed under experimental conditions, either with intentional operation trauma[9] or undergoing micromotion.[11,37,40–42] The observation is also in agreement with the findings of Piattelli et al,[14] who described the peri-implant tissues surrounding a failed Brånemark System implant with a similar clinical and radiographic appearance. Such a condition may be indicative of situations in which the host was unable to regenerate new bone around the implant; this might be explained by traumatic surgery, inadequate healing ability of the host, or micromotion at the interface.[7] It should also be considered that failed implants of patients B and D were placed in autogenous grafted bone.

Conversely, other asymptomatic, mobile implants (patients C, J, and Q) were characterized by a soft tissue capsule heavily infiltrated by a large number of inflammatory cells. In some instances, plasma cells prevailed toward the implant surface (patient Q), whereas epithelial downgrowth was observed around 2 implants (patients E and J) and was likely to have occurred also in specimen C. The possible causes for epithelial proliferation at the interface of submerged implants can only be speculated on. It is known that bacterial-derived lipopolysaccharide stimulates the expression of the proliferating cell nuclear antigen of the junctional epithelium.[43] This process is likely to be mediated by host cell–derived cytokines.[44,45] Alternatively, epithelial proliferation might have been stimulated by the disruption of the soft tissue interface induced by micromotion.[46] Since it is unknown whether micromotion influenced the implants analyzed in this investigation, such an explanation remains conjectural. It may also be speculated that bacteria and micromotion acted synergistically. Epithelial proliferation of a submerged implant in conjunction with a heavily infiltrated tissue rich in plasma cells and PMNs, in relation to a completely asymptomatic clinical condition, has not previously been described and might also be indicative of an asymptomatic infection. However, a clear histopathologic diagnosis of infection around recently inserted biomaterials may not be so immediate in the absence of appropriate microbiologic analyses.[47]

Another interesting ultrastructural observation was the presence of hemidesmosomes at the implant-epithelium interface of specimen E (Fig 2b). This is in agreement with early experimental findings in humans.[48] It is worthwhile to observe that this is the first time that the intact epithelium-titanium surface attachment has been described in a clinical situation.

Implants that failed after abutment connection and before prosthesis placement were characterized histologically by a heterogeneous interface, with areas of highly vascularized connective tissue and portions of bone. When bone was present, there was always evidence of detachment from the implant surface (erythrocytes). No other histopathologic description of this type of failure has been found in the literature, despite evidence that this condition is not so unusual.[8] The causes of these losses could have been multifactorial. Impaired healing, which had not been properly diagnosed, may be suggested for patient O. For patients F, K, and P, biomechanical disruption of a poorly mineralized interface could be considered. For some of these implants, "reosseointegration" may have been possible, if the implants had been left for longer healing. Sporadic case reports[49] (Sennerby et al, unpublished data) and experimental observations[37,50] seem to support the possibility of "reosseointegration."

Four of the failed implants were placed in grafted bone in 3 patients (B, D and K). In patients B and D, the implants were removed in conjunction with abutment connection, whereas in patient K they were removed 3 weeks after surgical exposure. Interestingly, the histologic picture, consisting of stratified connective tissue, was similar in all the examined material. Autopsy specimens of 6 stable Brånemark System implants obtained from a bone-grafted patient who died 4 months after implant surgery revealed minimal bone in direct contact with the implant.[51] Major portions of the implants were encapsulated in stratified connective tissue devoid of inflammatory cells, as observed in the present specimens. It is also known from the literature that implants placed in grafted bone are more likely to fail.[6] Therefore, an impaired healing ability of the grafted bone can be hypothesized as one of the primary reasons for the failure of these implants.

Implants with clinical signs of infection were retrieved at different time points. However, the decision to remove the implant was made by the responsible surgeon. The histologic picture of patient N was characterized by a strong inflammatory response and possibly epithelial proliferation, which is in agreement with an infection etiology. Such a condition has previously been described by others.[9,12,13,15–18]

Conclusions

The clinical, radiographic, and histopathologic pictures of the tissues surrounding early implant failures analyzed in the present investigation, taken together, indicated that infection (in patients who underwent complicated operations), impaired healing, and disruption of a weak bone-implant interface seem to be the major etiologic factors involved.

Acknowledgments

The financial support from the National Research Council of Italy (CNR), the Swedish Medical Research Council (9495), the Faculties of Odontology and Medicine at Göteborg University, the Swedish National Board for Technical Development (NUTEK), the C. M. Lerici Foundation, the Hjalmar Svensson Foundation, the Greta and Einar Asker Foundation, and the Adlerbertska Research Fund is gratefully acknowledged. We wish to thank Gunnel Bokhede, Lena Emanuelsson, and Ann Kristin Blomgren for their skillful technical assistance. The support of the staff at the Brånemark Clinic is greatly appreciated.

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