FOREIGN BODIES IN PROXIMITY TO FAILING DENTAL IMPLANTS

A Thesis

by

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ABSTRACT

Introduction: Recent studies suggest the potential role that foreign bodies play in the pathogenesis of implant failure. The aims of this investigation are: (1) to evaluate the presence of foreign bodies in proximity to failing dental implants that have been removed; (2) to examine the effect that these foreign bodies have on the surrounding hard and soft tissues.

Materials and Methods: A total of 21 patients possessing 34 dental implants were enrolled in this prospective, cross-sectional *ex vivo* study. Five of these 34 implants were removed for restorative reasons and were used as positive controls. A total of 6 implants (5 failed, 1 control) were assigned to group E (enzymatic digestion) and 28 implants (23 failed, 5 control) were assigned to group GS (ground section). Group E implants underwent enzymatic digestion in collagenase/dispase. Foreign bodies were isolated and imaged using Scanning Electron Microscopy (SEM) and Energy Dispersive X-ray Spectroscopy (EDS). Group GS implants were ground to 100 μm thick sections. Specimens were imaged using light microscopy, SEM, and EDS.

Results: One patient dropped out prior to implant removal, resulting in 33 total implants. Group E specimens primarily contained organic elements and minerals (carbon, oxygen, nitrogen, calcium, phosphorus, sodium, and chloride). Zinc was found in select specimens. Light microscopy of group GS revealed a greater number and size of titanium particles associated with failed implants. Titanium particles were commonly observed in proximity to soft tissue, demineralized bone, and inflammatory cells. Failed implants displayed surface delamination and bacterial colonies with accompanying titanium particles. Titanium particles were observed near the lumen of intrabony blood vessels in both failed and control implants. SEM and EDS of failed implants revealed countless titanium particles exfoliated from the implant surface. EDS of positive controls revealed the presence of titanium within the bone-implant interface.

Conclusion: A greater number and size of titanium particles are associated with failed implants when compared to controls. Titanium particles are correlated with bacteria, inflammation, implant surface delamination, and local vasculature. Implant surface distortion and titanium exfoliation may produce an environment that is not compatible with health.

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NOMENCLATURE

PMN	Polymorphonuclear leukocyte
RANKL	Receptor activator of nuclear factor kappa-B ligand
RANK	Receptor activator of nuclear factor kappa-B
AGE	Advanced glycation end product
BRONJ	Bisphosphonate related osteonecrosis of the jaw
MRONJ	Medication related osteonecrosis of the jaw
IL	Interleukin
TNF-α	Tumor necrosis factor-alpha
PDL	Periodontal ligament
TiO_2	Titanium Dioxide layer
CO_2	Carbon Dioxide
SEM	Scanning Electron Microscopy
Group E	Enzymatic digestion specimens
Group GS	Ground Section specimens

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1. INTRODUCTION AND LITERATURE REVIEW

Background and Significance

The field of dentistry and oral health has dramatically improved and evolved over the past few decades. According to the Centers for Disease Control and Prevention, the number of United States adults with complete tooth loss has decreased from 49 percent in 1960 to 13 percent in 2012.[1, 2] Additionally, elderly adults are motivated to maintain their dentition since tooth loss has an impact on their oral health-related quality of life.[3] Some benefits to having a full complement of teeth include improved esthetics, function, nutrient intake, and self-esteem. The number of people that are keeping their teeth is on the rise and when patients are missing certain teeth, they often choose to have them replaced.

One of the most challenging treatment goals in dentistry is the replacement of missing teeth. The traditional approach is to maintain the patient's existing dentition for as long as possible before resorting to tooth replacement options. Some of the conventional tooth replacement options are complete dentures, removable partial dentures, and fixed partial dentures. All of these options bring with them a rigorous maintenance and repair regimen. It has been known for some time that when a tooth is lost, the surrounding bone will gradually resorb in both height and width.[4] This has been referred to as disuse atrophy, which suggests that the body eliminates bone that is not actively stressed. According to Wolff's law, bone adapts its mass and structure to the mechanical demands placed on it.[4] These concepts raise concern for the dentist who is trying to maintain normal function of the dentition as well as prevent bone loss. A logical solution to this challenge is the use of dental implants, which will create mechanical stress on the bone in order to prevent bone resorption. While humans have attempted to replace natural teeth with implants for more than 1500 years, this did not become a reliable treatment option until the 1970's.[5, 6]

Early dental implant technology consisted of blade and transosteal implants, and it was thought that both of these implant types relied on mechanical retention.[7] A wide array of metals and implant designs were used unsuccessfully. One implant design that is frequently referenced is the subperiosteal blade implant developed by Dahl in the 1940's.[8] This implant was inserted between the bone and the soft tissue and therefore relied on soft tissue anchorage. These implants were fraught with complications and were typically removed soon after placement due to infection, inflammation, and foreign body response.[9] At the same time, further research was underway by Lee which involved implants inserted directly into the bone, referred to as endosseous implants.[8]

It was later discovered that a biological phenomenon takes place where the bone remodels and grows around the endosseous implant. This phenomenon was first described by Bothe in 1940 and by Leventhal in 1951, however, it was not until 1952 that P.I. Brånemark coined the term osseointegration.[6, 10, 11] Brånemark was studying blood flow in rabbits and discovered that titanium chambers placed in the rabbit tibia and fibula could not be removed from the bone. With this knowledge, he developed a dental implant fixture using pure titanium screws which had predictable long-term results.[12] This accidental discovery reinvigorated the field of implant dentistry and lead to the incorporation of implants into dental training programs.

Years after the original Brånemark implants were produced, Drs. Schroeder and Straumann of Switzerland worked with various alloys used in orthopedic surgery in order to develop their own dental implant.[13] In 1980, Schroeder initiated the International Team for Implantology (ITI) which helped stimulate advances in implant research and development. Several implant designs were developed and tested, including the Core-Vent, Stryker root form, and IMZ implants.[7] After years of testing, mainly through trial and error, some implants left the market and others withstood the test of time. The most popular dental implant designs used today are threaded, root-form implants with various surface treatments to facilitate osseointegration.

The original Brånemark implants had a smooth, machined surface, while most modern day implants have a roughened surface. The original Brånemark implants called

for a six-month healing time before loading while the modern day roughened surface implants can be loaded in as little as six weeks.[14] The roughened implant surface creates an increase in surface area allowing for increased bone apposition and better stress distribution along the implant body.[15] It has been shown that a roughened surface promotes bone formation by increasing the proliferation of cytokines, growth factors, and osteoblasts.[16] Some common surface treatments to create this roughened surface include sandblasting, acid etching, anodizing, electrochemical treatment, vacuum treatment, thermal treatment, and laser treatment.[17] Looking at these smooth and rough surface implants side by side, investigators have found that soft tissue tends to adhere more readily to a smooth surface while bone tends to favor a roughened surface.[18] This concept has led some implant companies to include a smooth collar at the top of their implant to facilitate soft tissue adherence.

A commonly used term in dentistry is biologic width, which refers to the soft tissue attachment to a tooth just above the level of the bone. This soft tissue barrier includes three main components: sulcus, epithelial attachment, and connective tissue attachment.[19] The biologic width serves as a seal between the bone and the outside world. In health, this soft tissue seal prevents bacteria and debris from causing bone loss around the tooth. With implants, the dentist tries to recreate this biologic width in order to prevent bone loss. Berglundh studied the biologic width around teeth and implants and found that while the epithelial attachment was similar, the connective tissue did not attach to the implant surface.[20] Other studies emphasized that the epithelium adheres to the implant via hemidesmosomes, as is seen with teeth, but the connective tissue encircles the implant without attaching to the implant.[21, 22] These results suggest that a tooth has a stronger biological seal than that of implants making the implant more prone to violation of this seal by bacteria and other debris.

Titanium became the material of choice for implants in both the dental and medical fields due to its biocompatibility and ability to osseointegrate. Biocompatibility is defined as the ability of a material to perform with an appropriate host response in a specific application.[23] Titanium is considered the most biocompatible metal due to its

resistance to corrosion from bodily fluids, inertness, and relatively high fatigue limit. A more real-world definition for biocompatible is an implant that is walled off in a tough, thin, avascular capsule that is quiescent.[24] Titanium does indeed follow this real-world definition.

A common misconception is that bone is in intimate contact with titanium. However, when a titanium implant is osseointegrated, bone is in close proximity to the implant, but does not adhere to it.[24] There is a thin biological layer between the bone and the implant, approximately twenty to fifty nanometers thick, referred to as the "zone of tolerance."[25, 26] This zone is composed of a titanium oxide layer, ground substance, and a cloud of zwitterionic forces that create enough friction to prevent movement of the implant. A zwitterion is a molecule that contains both a positive and a negative charge and therefore serves as a buffer between two dissimilar molecules. The titanium oxide layer is one of the key components that makes titanium biocompatible. The oxide layer insulates the titanium and serves as a buffer between the titanium and bone. Without a titanium oxide layer, titanium would become highly reactive and susceptible to corrosion.[24]

Dental implants are regarded as a safe and highly effective treatment option for replacing missing teeth.[24] Compared to the traditional tooth replacement options, dental implants have several benefits. Implants help maintain the bone level, they prevent the need for drilling on adjacent teeth, and they provide a fixed restoration. This allows for superior esthetics and function when compared to alternative tooth replacement options. However, many dentists have been under the false pretense that implants are the cure-all to restoring the patient's dentition. This has resulted in dentists removing teeth that are in a less than ideal condition in order to replace them with implants. This sounds good in theory, but it relies heavily on the assumption that implants are a safe long-term solution.

Due to the large number of implants being placed by a wide array of dental professionals, the modern dentist is faced with multiple implant complications. Giannobile published an article entitled "Are Dental Implants a Panacea?"[27] This article discusses the trend in dentistry to remove teeth that could have been salvaged in order to replace them with a "newer, better" implant. Giannobile provides several references

supporting the notion that even a severely compromised tooth may have longevity that far surpasses that of the average dental implant.[28, 29] Furthermore, Derks *et al.* made a bold argument that forty-five percent of implant patients have peri-implantitis.[30] The authors aggressively defined peri-implantitis as an implant with bleeding on probing and greater than 0.5 mm of bone loss. Literature would typically categorize this scenario as a healthy implant.[31] Nonetheless, Giannobile, Derks, and others[32] have made stark statements about implants in order to prove a point. Dental implants should not be regarded as a panacea and they certainly are not immune to complications.

Currently active implant companies have commercialized and simplified the process of implant placement and implant restoration. Also, there is an incredibly high profit margin with implants, market driven, which could result in a biased treatment plan. The original Brånemark implants were typically placed in a sterile operating room setting by oral and maxillofacial surgeons, while today, most implants are placed in a private practice setting by a variety of dental professionals. Countless continuing education courses and dental school curricula include training on the placement and restoration of dental implants. As a result, implants are being placed and restored by individuals with varying educational backgrounds. According to Adell, inexperienced surgeons had a 5-year implant survival rate of 75 % while experienced surgeons had a 5-year survival rate of 98 %.[33] Lambert found that inexperienced surgeons had implants fail twice as often as experienced surgeons.[34] Da Silva conducted a practice-based research network study where implant parameters were measured over time in multiple general dentists' offices.[35] The study found that after four years, seven percent of the implants were classified as failures and 18.7 percent were considered to have excessive bone loss. The authors concluded that general dentists have a higher implant failure rate when compared to the failure rate of specialists.

The pioneers of implantology have indeed paved a wonderful path with a promising future, but it is important to acknowledge that implants can lead to major complications in the oral cavity. In an effort to standardize the evaluation of implant health, Albrektsson *et al.* formulated the criteria for implant success in 1986.[31] The criteria

include: 1) immobility of the implant; 2) a lack of peri-implant radiolucency on a radiograph; 3) less than 0.2 millimeters vertical bone loss after the first year of service; 4) absence of pain, infection, neuropathy, paresthesia, or violation of the mandibular canal; and 5) a minimum success rate of 85 percent at five years and eighty percent at ten years. The authors also stated that 1.5 millimeters of crestal bone loss within the first year would be considered a success as this may be due to the body establishing a biologic width around the implant.

Implant design has changed significantly since the Albrektsson publication in 1986. Most modern-day implants utilize a design known as platform switching in order to maintain the bone level over time. Platform switching is when an implant is restored using an abutment that is of narrower diameter than the implant diameter. For example, if the implant is six millimeters in diameter, the portion of the crown that is attached to the implant is four millimeters in diameter. This concept was accidentally discovered when 3i Implant Innovations used abutments that were narrower than their implants. Lazzara and Porter reported that less bone loss was seen with platform switching.[36] This is based on the concept of osseointegration of a roughened titanium surface and the concept of biologic width. The platform switch allows for the bone to osseointegrate to the very top of the implant without a separate restorative component impinging on this bone to implant connection. This also will allow the body to create a biologic width around the abutment and crown as opposed to it occurring on the implant itself. Due to platform switching, in contrast with platform matching, one can expect to have less bone loss after implant restoration.[37, 38]

According to recent studies, platform switched implants have minimal bone loss in the first year of service, and bone will even grow back to the coronal portion of the implant over time. Chrcanovic reported on Nobel implants that had been followed for twenty years and found that eleven percent had a gain in bone height and thirty-six percent had bone loss less than one millimeter.[37] Froum found an average of 0.8 millimeters of bone loss after one year, which decreased to only 0.3 millimeters of bone

loss at eight years.[39] These results are encouraging and are clearly superior to the expectations proposed by Albrektsson.

When an implant does not meet the Albrektsson criteria for success, it is typically diagnosed with some form of peri-implant disease. Implants with peri-implant disease are categorized by the American Academy of Periodontics as having either peri-implant mucositis or peri-implantitis.[40] Peri-implant mucositis entails the inflammation of the soft tissue around an implant without the loss of bone.[41] Peri-implantitis involves inflammation of the soft tissue and progressive bone loss around the implant. According to a systematic review by Atieh *et al.*,[42] peri-implant mucositis affects 63% of implant patients while peri-implantitis affects 19% of patients. In order to aid the clinician in determining a prognosis of a diseased implant, Froum *et al.*[43] have classified peri-implantitis into three different categories: early, moderate, and advanced. Early peri-implantitits is defined as an implant with a periodontal probing depth of greater than four millimeters, with bleeding upon probing and bone loss of less than 25 percent of the implant length. Moderate peri-implantitis entails probing depths from six to eight millimeters with bleeding upon probing and 25 to 50 percent bone loss. Advanced peri-implantitis is an implant with a periodontal probing depth of greater than eight millimeters, with bleeding upon probing and bone loss of greater than 50 percent of the implant length.

Peri-implantitis can eventually result in implant failure, which usually requires surgical removal of the implant in order to prevent further pain, infection, and bone loss. Becker *et al.*[44] described implant failure as the presence of implant mobility and radiolucency around the implant. While this is a broad definition, several other clinical observations such as pain, infection, tissue inflammation, and degree of bone loss help the clinician determine whether the implant is salvageable or needs to be removed.

Several studies have evaluated factors that could contribute to implant failure, yet in many cases the cause remains unknown. The timing of implant failure and an understanding of the healing process are useful tools that aid the clinician in determining the potential causes of failure. Chrcanovic *et al.*[45] define primary, or early, implant

failure as an implant that fails to osseointegrate after it has been placed in bone (i.e., failed to form a close union between the implant and surrounding bone during healing). Some studies speculate that primary implant failure could be due to overheating of the bone and/or poor surgical technique, however, they have not shown a cause and effect relationship.[46, 47]

Chrcanovic *et al.*[45] state that secondary implant failure occurs later than primary implant failure and is due to progressive bone resorption around the implant (i.e., advanced peri-implantitis). Studies show that bone loss around an implant could be associated with one or more of the following: poor clinical handling, poor implant design, complex patient medical history, poor oral hygiene, overloading of the implant due to the crown being too high, excess cement, or a response to foreign particles embedded in the tissue.[45, 48-51] Some of the clinical parameters for secondary implant failure include deep probing depths (using a periodontal probe), bleeding upon probing, purulence, pain upon palpation or percussion of the area, and radiographic bone loss.

Risk Factors for Implant Disease

The literature discusses several patient-related risk factors that must be considered when studying implant disease. Smoking and its relationship to periodontal destruction has been discussed extensively in the literature.[52, 53] A longitudinal study by Miller *et al.* conducted statistical analyses of several variables that may contribute to tooth loss and found that smoking was the most important risk factor for tooth loss.[54]

Several mechanisms by which smoking affects wound healing are discussed by Rivera-Hidalgo.[55] Nicotine decreases the proliferation, attachment, and chemotaxis of periodontal fibroblasts. Fibroblasts are a key cell that function in the healing and turnover of periodontal tissues. Smokers also have a decrease in oxygen delivery to the periodontal tissues which leads to an increase in anaerobic bacteria. One of the key immune cells, the polymorphonuclear leukocyte (PMN), aids in preventing periodontal destruction. In smokers, these PMN cells have decreased motility and function. Smokers

typically experience severe xerostomia, or dry mouth, which allows an increase in bacterial adhesion to the soft tissue and inadequate salivary flushing mechanisms. The small capillary network in the soft tissue shows less perfusion of blood to the tissue in smokers. This means that the tissue is unable to receive enough nutrients and it is unable to rid itself of waste products. Budunelli *et al.* found that smokers have an altered RANKL to osteoprotegrin ratio.[56] RANKL is an acronym for receptor activator of nuclear factor kappa-B ligand, which binds to RANK in order to trigger bone resorption. Osteoprotegrin is a protein that can bind RANKL in order to minimize its effects. Simplistically, this means that in smokers, the signaling molecules are allowing for bone destruction as opposed to bone formation. Finally, an increase in advanced glycation end-products (AGEs) results in a decrease in oxygen delivery to the tissues and a decrease in collagen turnover.[57]

The literature clearly demonstrates the detrimental effects of smoking to the periodontium. Smoking appears to have a similar impact on dental implant health as well. Karbach *et al.* found that smoking was the most important risk factor for the formation of peri-implant mucositis.[58] It has also been shown that bone loss around implants in smokers is twice that observed in nonsmokers.[59] Another study that looked at long-term results of implants found that the rate of implant failure was higher for smokers than for non-smokers.[60] The authors concluded that the higher failure rate in smokers was due to a reduced healing capacity.

The modified implant surface may have a beneficial effect for smokers. One study compared machined implants and oxidized implants in smokers and nonsmokers.[61] The authors found that with machined implants, smokers lost twice as much bone as nonsmokers. However, with oxidized implants, smokers and nonsmokers showed similar bone levels and failure rates. Balshe and coworkers found that rough surface implants in smokers had no significant failure rate, but the failure rate was significant for smooth surface implants.[62] Chung *et al.* studied a variety of implant designs in smokers and nonsmokers placed over a 21-year period.[63] They found that smokers had almost three times more annual bone loss than nonsmokers. While some studies show reassuring

results with rough surface implants, smoking is still considered a risk factor for peri-implant disease.

A large body of literature discusses the effects of diabetes mellitus on periodontal health.[64, 65] Many of these studies state that there is a bidirectional relationship in which the stability of one disease influences the other. Löe was the first to suggest that periodontal disease is the sixth complication of diabetes.[66] Some of the common complications found in diabetics include cardiovascular disease, neuropathy, nephropathy, retinopathy, and vascular changes. When a patient has prolonged elevated blood glucose, there is an increase in advanced glycation end-products (AGEs), which results in diminished oxygen delivery to tissue and poor collagen turnover. There is also a decrease in PMN leukocyte motility and function, decreased fibroblast function, and increased RANKL/osteoprotegrin ratio.[65] Some of these detrimental changes are similar to those seen in smokers and will undoubtedly have an effect on bodily function and on healing capacity. A patient with well-controlled diabetes will typically have fewer of these sequelae and will hence heal better than an uncontrolled diabetic.

For both periodontal therapy and implant therapy, it is believed that a well-controlled diabetic (Hemoglobin A1C $\leq$ 7) will fare well during the healing stages.[67] Lab studies have shown that diabetic pigs have less bone-to-implant-contact and that rats injected with AGEs exhibit a slower rate of osseointegration.[68, 69] Another study on diabetic rats found decreased bone density around the implants.[70] Studies in humans have found a correlation between uncontrolled diabetes and bleeding upon periodontal probing around implants, but they did not report an increase in bone loss or implant failure among diabetics.[71-73]

Osteoporosis is known for causing a decrease in bone density and is typically found in postmenopausal females.[74] In general, multiple cohort and meta-analysis studies have found a slight correlation between osteoporosis and implant failure, but the correlation is weak and not statistically significant.[75, 76] Many osteoporosis and cancer patients are prescribed bisphosphonates, which decrease bone loss by inhibiting osteoclasts. Osteoclasts are bone cells that degrade bone into its mineral components and osteoblasts

are bone cells that deposit new bone. Both of these cells are synergistically essential for bone turnover and bone healing. Without the help of osteoclasts, the jawbone is lacking in healing capacity and is therefore susceptible to a condition known as bisphosphonate-related osteonecrosis of the jaw (BRONJ). Several other medications, such as RANK ligand inhibitors and antiangiogenics induce a similar phenomenon and so the term has been changed to medication-related osteonecrosis of the jaw (MRONJ).[77]

MRONJ is typically encountered when an oral surgery procedure is done that relies on the healing capacity of the jawbone. Certain bisphosphonates, such as intravenous (IV) and nitrogen-containing oral bisphosphonates, are associated with a higher incidence of MRONJ.[77] Shabestari *et al.* conducted a case series on 21 patients taking oral bisphosphonates and found that bisphosphonates had no effect on implant health.[78] A retrospective study on 362 patients treated with dental implants found no correlation between bisphosphonates and implant failure, but there was a correlation with implant thread exposure over time.[79] The use of implants in patients taking oral bisphosphonates has been shown to be relatively safe, but it is ultimately up to the clinician to determine if the patient is a candidate for dental implant therapy.

Radiation therapy is often administered for the treatment of head and neck cancer.[74] This treatment can result in severe dry mouth and altered function of the bone and soft tissue. Oftentimes, physicians will recommend hyperbaric oxygen therapy prior to surgical procedures in order to enhance healing capacity. Similar to MRONJ, a history of radiation therapy can result in a condition known as osteoradionecrosis of the jaw. A systematic review including 10,150 implants found that implants placed in irradiated bone had a 174 percent higher chance of failure.[80] The authors found no correlation with hyperbaric oxygen therapy and improved implant success.

A commonly discussed risk factor for implant disease is periodontal disease. Periodontal disease has a wide array of causes and risk factors, but is most commonly associated with bacterial plaque and the host immune response.[81] Periodontitis and peri-implantitis are both typically associated with a certain bacterial profile, namely, gram-negative anaerobic bacteria.[82] In addition, certain patients may be more susceptible to

deterioration of the periodontium due to countless variables such as medical history, social history, bacterial flora, and genetic profile.[81]

A cross sectional study including 109 volunteers found implant failure to have a significant correlation with periodontitis.[83] Swierkot *et al.* conducted a prospective long-term study on patients with a history of generalized aggressive periodontitis, formerly known as juvenile periodontitis.[84] Despite the fact that the aggressive periodontitis was controlled prior to implant placement, it was found that these patients were more susceptible to peri-implantitis, peri-implant mucositis, and implant failure when compared to healthy control patients. Another longitudinal cohort study on adults found a significant correlation between severe chronic periodontitis and late implant failure.[85] Costa *et al.* found that when patients with peri-implant mucositis did not attend regular maintenance appointments, they were much more likely to develop peri-implantitis.[86] These authors again found a significant correlation between periodontitis and peri-implantitis.

Based on these findings, the dental professional must remain abreast of current research with regard to risk factors for developing implant disease and implant failure. Smoking, diabetes mellitus, antiresorptive therapy, antiangiogenic therapy, radiation therapy, and periodontal disease are some of the more common risk factors discussed in the literature. Of these risk factors, several studies suggest that smoking and periodontal disease are the most prevalent risk factors for developing implant disease.[82, 83, 85, 87]

Etiology- Bacterial Plaque

One of the most controversial and highly studied questions in dentistry is "what causes implant disease?"[41, 42] As with teeth, the cause of implant disease is typically regarded as multifactorial. Assuming that all risk factors are controlled and the patient is healthy, the patient is still prone to developing implant disease or implant failure due to a plethora of etiologies.

A commonly discussed primary etiology for gingivitis and periodontitis is bacterial plaque.[81] This has resulted in extensive research on the role that bacterial plaque plays in peri-implant diseases. The formation of a well-organized biofilm on an implant has been shown to be capable of initiating and propagating peri-implant disease.[41] The mechanism by which this occurs is considered to be similar to that with teeth. Peri-implant mucositis can develop in a similar manner as gingivitis and peri-implantitis can develop in a similar manner as periodontitis. The early stages involve soft tissue inflammation and a shift from gram-positive aerobic bacteria to gram-negative anaerobic bacteria. If this early lesion is left unclean and uncontrolled, the plaque matures and the inflammation can progress resulting in bone loss.

In 1965, Löe was able to demonstrate in humans that the accumulation of bacterial plaque on teeth leads to gingivitis and that gingivitis resolves once oral hygiene is reinstituted.[88] Pontoriero *et al.* conducted a similar study on implants, using teeth in the same patients as a comparison.[40] After three weeks of plaque accumulation, the teeth and implants both displayed similar changes in bleeding, swelling, probing depth, and bacterial profile. There was no statistically significant difference between the teeth and implants after plaque accumulation. The teeth developed gingivitis as expected and the implants developed peri-implant mucositis. One criticism with this study is that the authors did not take measurements after the patients resumed oral hygiene and therefore did not demonstrate whether peri-implant mucositis is a reversible process. Salvi et al. conducted a similar study and included clinical measurements three weeks after reinstitution of oral hygiene.[89] Gingivitis and peri-implant mucositis were found to be reversible at the biomarker level, but the clinical parameters had not yet reached the pre-experimental levels. These parameters did however show trends toward resolution in both teeth and implants.

The term peri-implantitis was first used by Mombelli in 1987 when he discovered that implants with bone loss harbored gram-negative anaerobic rods, black-pigmented bacteroides, fusobacterium species, and spirochetes.[90] When evaluating the microbiota of healthy implants in the same patients, Mombelli saw predominantly coccoid cells. He

referred to peri-implantitis as a site-specific infection, which has many features in common with periodontitis.

Peri-implantitis is thought to be initiated in a manner similar to periodontitis, namely by a mounting bacterial insult and a host response.[41, 42] Some studies show a similar bacterial profile for both peri-implantitis and periodontitis, while others show a unique profile for peri-implantitis.[91] An independent study group of thirty clinical experts met in Italy to systematically review the literature on peri-implantitis.[91] They concluded that peri-implantitis is not comparable to periodontitis since several anatomical differences exist between the periodontium and the peri-implant environment. The review supported studies that showed peri-implantitis to have gram-negative anaerobes, opportunistic microbes, Epstein-Barr virus, anaerobic gram-positive rods, and *Staphylococcus aureus*. Some have suggested that *S. aureus* is the microbe that initiates peri-implantitis, but this notion was refuted by the aforementioned review in Italy.[92, 93]

Periodontitis and peri-implantitis have also been shown to have a similar inflammatory cascade.[41] They both show an upregulation of proinflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-12, and tumor necrosis factor (TNF)-α.[41] However, one key difference is that peri-implantitis typically progresses more rapidly than periodontitis. Based on the studies of osseointegration and biologic width around implants, the protective barrier around implants is not as resilient as that found around teeth. Teeth have a connective tissue attachment and inserting collagen fibers along the root, while implants lack connective tissue attachment and simply have an avascular space between the implant and the bone. A recent comparison claimed that teeth have a self-limiting process where a protective connective tissue capsule separates the lesion from the bone.[94] This process was not found with implants and the lesion extended into the bone.

Most modern implants have undergone some sort of surface modification and therefore have a rough surface. This surface provides a niche for bacterial plaque to firmly attach to the implant and therefore create a mature bacterial colony.[95] Ultrasonic and hand instruments can usually remove the majority of plaque from a tooth, but they

usually do not remove all of the hard deposits known as calculus.[96] With implants, removal of bacterial plaque and calculus can be even more challenging simply due to the topography of the implant surface. This poses a challenge for the clinician once the bacterial plaque has reached the implant itself. Some implant companies supply "tissue-level" implants that have a polished collar at the very coronal portion of the implant. This polished titanium is much easier to clean and allows for soft tissue adhesion. The drawbacks with this design are poor esthetics and difficulty creating a properly shaped crown as it emerges from the implant.

Etiology- Occlusion

Occlusion is another potential etiology for implant disease and implant failure. Occlusion has been studied extensively on teeth, but there is still a paucity of evidence regarding occlusion on implants.[97] A tooth is suspended within its bony housing by the periodontal ligament (PDL). The PDL serves as a shock absorber which distributes forces along the root.[98] The PDL also contains mechanoreceptors, which allow the patient to feel if they are chewing too hard on a tooth. Implants on the other hand lack a PDL and are simply in close proximity to the bone. Implants therefore lack the shock absorber effect of the PDL and do not move or give when the patient is chewing. This results in a concentration of forces at the crestal bone around implants.[98] A tooth can move 25 to 100 micrometers (μm) in the vertical direction and 56 to 150 μm horizontally. Implants can move 3 to 5 μm vertically and 10 to 50 μm horizontally. Implants also produce less tactile sensation and occlusal awareness.[99] The clinician is therefore faced with the challenge of creating a fine-tuned occlusal scheme that prevents excessive forces when the implants are in function.

According to Wolff's law, the bone adapts to the mechanical stresses placed on it.[4] Frost found that this could result in either bone deposition or bone resorption depending on the direction and magnitude of the forces.[100] He found that a very low amount of strain on the bone could result in disuse atrophy of the bone. A mild amount of strain

allows for a "steady state" of bone damage and bone repair. However, an increased level of strain resulted in bone resorption and even bone fracture.

When teeth are exposed to excessive occlusal forces, this is known as occlusal trauma. This may result in bony changes, occlusal wear, widened PDL, and tooth mobility.[101] With implants, the appropriate term is occlusal overload. This occurs when either normal function or parafunctional habits result in structural or biological damage.[102] Occlusal overload can result in damage to the prosthesis, implant, or surrounding bone. Many have suggested that peri-implantitis and occlusal overload are the two most common causes of late implant failure.[97]

Implant studies state there is a possible relationship between occlusal overload and crestal bone loss, but that it depends on other factors as well.[103] Kozlovsky *et al.* demonstrated in a dog model that occlusal overload with uninflamed mucosa resulted in a slightly reduced marginal bone level.[104] However, bone loss beyond the implant neck only occurred when both occlusal overload and peri-implant inflammation were present.

Some of the more common encounters seen with occlusal overload are prosthetic screw loosening, screw fracture, prosthesis failure, and implant fracture.[105, 106] Implant fracture can lead to peri-implant bone loss resulting in complete implant failure.[107]

In order to prevent costly implant repair and replacement procedures, an ideal occlusal scheme must be created to maximize implant longevity. Based on studies by Wolff and Frost, it makes biomechanical sense to minimize the amount of cantilever forces in the prosthetic design.[4, 100] In other words, it is preferable to have biting forces that are primarily in a vertical direction as opposed to torqueing forces that are pushing heavily on a specific side of the implant. Cantilever forces are minimized by using an implant prosthesis that is slightly narrower than a normal tooth. It is preferable to have a prosthesis that does not extend too far in any direction beyond the diameter of the implant itself.[97] The cusp inclination in the design of the crown can also result in non-axial shearing forces when in function.

Crown to implant ratio is a topic that is debated in the literature.[108] Many authors have found equal success rates when using short versus long implants, while others have

found inferior results with short implants.[109, 110] A common argument is that since the majority of the forces are at the coronal portion of the implant, then the apical portion must not matter. A consensus to this debate remains to be seen, but most clinicians and implant companies prefer implants that are at least eight millimeters in length.[111]

When the patient is in maximum intercuspation (i.e., biting down), the implant crown should have very light or no occlusal contact with the opposing tooth.[107, 112] This is done to compensate for the lack of PDL around the implant. When a patient goes from a normal bite to a heavy bite, the PDL will allow the teeth to compress, but the implant will remain stationary. In addition, when the patient is moving their jaw in a lateral or excursive direction, there should be no contact on the implant crown.

Parafunctional habits must also be considered during implant therapy. Patients who brux (grind their teeth) or clench their teeth have a higher risk of implant failure.[113] These patients may benefit from wearing an occlusal night guard in order to prevent excessive forces from parafunctional habits. For both teeth and implants, a favorable occlusal scheme can have a large impact on the wear patterns that are seen after years of function.

Etiology- Surgical Technique

Another potential etiology for peri-implant disease is the clinical technique used for implant therapy. A great deal of demand for dental implant treatment exists among dental professionals and among the public as well. This has led clinicians to use implants in unique and innovative ways that do not follow the aforementioned biological and mechanical principles.

If the implant is not placed into bone of sufficient quality and quantity, the implant will be at a much higher risk for failure.[111, 114] Primary stability is a requirement for osseointegration to occur. If the implant is mobile at the time of placement, it will be at risk for failure. Leckholm and Zarb developed a bone classification system to aid the clinician in implant planning.[115] Type I bone is compact cortical bone, type II is dense

trabecular and cortical bone, type III is dense trabecular bone with thin cortical bone, and type IV is low-density trabecular bone surrounded by thin cortical bone. Seibert created a classification system for the shape of the defect in edentulous sites.[116] A class I defect entails a loss of defect width, class II is a loss of defect height, and class III is a loss of both width and height. The maxilla typically has less dense bone than the mandible and the posterior jaws are typically less dense than the anterior regions. As a result, the mandible typically has higher implant success rates and the posterior maxilla has higher failure rates.[117]

The condition of the soft tissue is another critical variable for implant therapy. The biologic width around implants is less than ideal and so the quality and quantity of soft tissue can play a role in implant health. With teeth, a lack of keratinized tissue (gingiva) can result in inflammation, recession, and even tooth loss.[118] With implants, the topic of keratinized mucosa is controversial due to a lack of sufficient evidence. Wennström demonstrated that health can be maintained around both implants and teeth that do not have keratinized mucosa.[119] It must be noted that these results were obtained in patients with adequate homecare and periodic professional cleanings. Others have found that while a lack of keratinized mucosa does not affect implant survival, there is a greater degree of plaque accumulation and mucosal inflammation.[120] Block *et al.* found that a lack of keratinized mucosa is associated with crestal bone loss of two millimeters or more and that keratinized mucosa is directly correlated with soft and hard tissue health.[121] Therefore, a lack of keratinized mucosa could be an anatomical or surgical flaw that affects implant health.

Surgical trauma during implant placement should be minimized in order to maximize the likelihood of proper healing. Bone is a living tissue, sensitive to heat, and overheating of bone during preparation of the site for an implant can lead to necrosis.[122] The clinician must use the proper drilling sequence and cooling mechanisms in order to minimize trauma to the bone. Occasionally, the surgeon will inadvertently create a fenestration in the bone resulting in the implant being in contact with soft tissue during

healing.[111] This situation can have a direct impact on whether or not osseointegration will occur.

An aseptic surgical field will help minimize bacterial contamination and will result in lower implant failure rates as well.[111] It is recommended that the surgeon use sterile instruments, proper draping, and careful handling of the implant after removal from its package.

A popular surgical technique is the flapless approach to implant placement. This technique typically entails creating a small hole in the soft tissue and then preparing the implant bed through this hole. The benefits to this approach are less post-operative pain and less trauma to bone and soft tissue.[111] Many believe that this will result in better healing and esthetics. Froum *et al.* conducted a study comparing flapless and flap protocols for implant placement.[39] After eight years, they found no difference in bone levels, probing depths, bleeding on probing, or papilla height. The authors concluded that both protocols were successful. With advances in radiology and three-dimensional implant planning, it is feasible to use the flapless protocol as long as proper surgical technique is exercised.

Implants can be placed using a one-stage or a two-stage protocol. The one-stage protocol entails placing an implant and a transmucosal healing abutment at the same time. This allows the implant to osseointegrate and it allows the tissue to heal around the abutment. With the two-stage protocol, the implant is buried underneath soft tissue and later uncovered for attachment of a healing abutment. The benefits to the one-stage protocol are reduced time, money, and surgical trauma.[111] The healing abutment also allows for the early formation of a biologic width while the implant is healing. The drawbacks to the one-stage protocol are the potential for bacterial contamination of the implant during healing and the potential for trauma to the implant by the patient. With the two-stage protocol, the implant is allowed to completely integrate prior to its exposure to the bacterial flora and mechanical forces of the oral cavity. Several studies show a decreased risk of implant failure using the two-stage protocol, but the clinician must decide whether it is worth the additional time, money, and surgical trauma.[123, 124]

Another surgical technique that is commonly used involves placing the implant into a fresh extraction socket, referred to as an immediate implant.[111] This treatment can be beneficial to the patient since it entails one less surgery and the patient can have the tooth replaced by an implant sooner than conventional therapy. The drawbacks to this procedure are increased risk of infection, low bone to implant contact, more bone resorption and higher risk of implant failure.[125] The tooth extraction procedure causes trauma to the bone and surrounding soft tissue, and implant placement on the same day will further traumatize this bone. This is why studies have shown an increase in bone resorption and failure rate with immediate implant placement versus delayed implant placement.[126] A benefit to immediate implants that is worth noting is the ability to create a temporary crown or custom healing abutment on the implant. This will help preserve the soft tissue dimensions that were present around the tooth prior to extraction. Nonetheless, immediate implant placement is a potential etiology for implant failure.

Some teeth that require removal present with a lesion around the apex of the root, known as a periapical lesion. Many dentists have successfully placed immediate implants in sockets where periapical lesions exist. The goal is to thoroughly debride and clean the lesion prior to implant placement. Randomized controlled trials have shown similar failure rates when implants were placed immediately in sockets with periapical lesions.[127, 128] However, there is a high likelihood of not obtaining primary stability, which is critical for osseointegration. Interestingly, a periapical lesion on a tooth adjacent to the implant creates a higher risk for infection around the apex of the implant.[129] Without proper site preparation, placing an implant into a site of active infection will pose a risk for implant infection and failure.

Etiology- Cement

The prosthetic components that attach to an implant are typically made up of an abutment, which screws directly onto the implant, and a crown or bridge prosthesis. The prosthesis can either be cemented onto the abutment in the clinic or the prosthesis and

abutment can be fabricated as one piece in the lab. This one-piece prosthesis is referred to as screw-retained since it can be screwed directly into the implant itself without the need for dental cement. Both cement and screw-retained prostheses are used routinely in the dental office, but some dentists prefer the cement-retained approach since it is typically more affordable. Also, the screw-retained prosthesis has a hole in the final crown for access to the screw. The location of the screw access hole relies heavily on proper implant placement so that the hole does not affect the cosmetics or function of the restoration.

The drawbacks to a cement-retained prosthesis are that the crown is difficult to remove once it has been cemented into place and there is a potential for excess cement to extrude into the surrounding tissue as the prosthesis is seated. This excess cement is very difficult to remove and can be inadvertently left embedded in the soft tissue. In 1999, Pauletto *et al.* reported on four cases where excess cement was associated with inflammatory lesions around the implants.[130] Deep probing depths, bone loss, and purulence were noted during surgical removal of the excess cement, and the lesions resolved after cement removal. Another case report demonstrated implant failure that occurred one month after crown cementation.[131] During surgical removal of the failed implant, significant bone loss was found adjacent to an area with excess cement and inflamed granulation tissue. Wilson conducted a case-control study where he compared 42 test implants with peri-implantitis to twenty healthy control implants.[48] He used a dental endoscope to explore the condition of the peri-implant mucosa. Excess cement was found in none of the controls and in 34 of the test sites. Thirty days after removal of excess cement, 25 of 33 test sites had no clinical signs of inflammation. The author concluded that excess cement was associated with peri-implant disease.

Burbano *et al.* studied nineteen human biopsies that were taken from implants with peri-implantitis and cement-retained crowns.[51] The biopsies were analyzed using scanning electron microscopy and elemental analysis in order to determine the presence of dental cement embedded in the soft tissue. All nineteen of the specimens displayed the presence of cement, which were correlated with five different commercially

available cements. Penarrocha-Oltra *et al.* studied the presence of different bacteria present around screw-retained and cement-retained implants.[132] After sampling 55 cement-retained implants and 46 screw-retained implants, the authors found a significantly higher bacterial load in the cement-retained group.

An *in vitro* study by Rodriguez *et al.* studied the effects that different dental cements have on human gingival fibroblasts (soft tissue forming cells) and on preosteoblasts (bone forming cells).[133] The various dental cements had only a minor effect on the preosteoblasts, but they had a significant effect on the fibroblasts. There was a statistically significant decrease in the number of human gingival fibroblasts when exposed to all cements except for one. The one cement that had less of an effect on fibroblasts contained zinc oxide noneugenol, with the trade name "Temp-Bond." Three different controlled clinical studies found no correlation between cement-retained crowns and implant failure.[134-136] However, cement remnants are associated with soft tissue inflammation, increase in bacterial load, and bone loss around the implant. Excess cement may have an effect on implant health, but not necessarily on implant failure.

Etiology- Titanium Allergy

Titanium is regarded as extremely inert and biocompatible, and many are unaware of the possibility for an allergic reaction to titanium. There is a body of evidence, albeit limited, that reports on allergic reactions to titanium.[137] The most common allergic reactions to titanium include types I, III, and IV. With type I hypersensitivity reactions, the patient has been previously exposed to the allergen (i.e., titanium) and will mount a specific immune response to the allergen using IgE antibodies. This is the classic allergic reaction and it typically occurs in a short period of time. Type III hypersensitivity reactions occur when there is an excess of antigen-antibody complexes and the body is unable to clear them from the affected area. This type of reaction can take days or weeks to develop. Type IV hypersensitivity reactions are different in that they are cell-mediated and not antibody-mediated. This reaction occurs when T helper cells recognize the

allergen and secrete cytokines that cause a chain of events to occur. Eventually, the environment is filled with various destructive cells such as macrophages, T lymphocytes, and mast cells that can cause damage to the surrounding area. Type IV reactions are delayed and take several days to develop.

With orthopedic implants, several studies have reported an allergic reaction that caused the titanium implant to fail.[137] One study reported on patients that became symptomatic after placement of titanium plates for fixation of bone fractures.[138] Microscopic analysis revealed the presence of T lymphocytes and macrophages indicative of a type IV reaction. The tissue adjacent to the titanium appeared discolored and further analysis revealed titanium embedded in the tissue. Another study reported on tissue samples from patients that had failing prosthetic hips.[139] T cells and macrophages were again present in the tissue indicative of a type IV allergic reaction. Interestingly, all five of these patients revealed a negative result to a skin patch test using titanium. However, a titanium ointment test yielded positive results in two of these patients.

In the dental literature, a variety of allergic reactions to titanium have been reported. A cohort study in Spain evaluated 1500 implant patients for potential titanium allergies.[140] Thirty-five of these patients were suspected of having a titanium allergy based on a history of multiple allergies and a clinical appearance of an allergic reaction. Sixteen of these patients displayed allergic symptoms after implant placement or unexplained implant failure. Nine of these patients displayed positive reactions to titanium allergy tests. Based on these findings the authors gave an estimated prevalence of titanium allergy of 0.6 percent.

Some implant systems utilize a titanium nitride-coated implant abutment.[141] One case report discussed an allergic reaction to this coating, which resolved after removal of the titanium nitride abutment. Another article reported on a 41-year-old woman who experienced exfoliative cheilitis (exfoliation of the lips) after implant placement.[142] A third case reported on a patient that experienced facial eczema after placement of two mandibular implants.[143] The eczema resolved after removal of these implants. Titanium oxide is used as an additive in dermatological products, toothpaste, icing, salad dressing,

chewing gum, candy, milk, tattoo ink, and paints with the general consensus that it is safe.[144] Based on this limited evidence, one can surmise that titanium allergies do occur, but are rare.

Etiology-Foreign Body Reaction

A titanium implant is considered a well-tolerated foreign body, but is a foreign body nonetheless. The roughened surface, the titanium oxide layer, and the "zone of tolerance" between the bone and the implant allow for equilibrium to exist between the implant and the human body.[145] In some cases this equilibrium is shifted from normal osseointegration to a foreign body reaction. Nowzari *et al.* compared the levels of periodontal pathogens and pro-inflammatory cytokines around healthy teeth and healthy implants.[146] The authors found more periodontal pathogens around healthy teeth yet they found approximately twice as many pro-inflammatory cytokines around healthy implants. The prominent cytokines around implants were IL-1ß, IL-6, IL-8, and TNF-α. For both teeth and implants, the cytokine levels were higher when bacteria were detected.

With failing dental implants, it is difficult to prove if a foreign body reaction occurs since bacterial plaque is present as well. Orthopedic implants however are placed in a sterile field and are isolated from the outside world. These implants do occasionally lose osseointegration without an explanation other than a "foreign body reaction."[147] Albrektsson *et al.* claim that initial marginal bone loss around implants is a reaction to treatment and not a disease process.[148] They state that the initial foreign body response can be sustained and aggravated leading to significant bone loss and implant failure. In these cases, once severe bone loss has occurred, a secondary bacterial infection may follow. The authors state that marginal bone loss around an implant should not be regarded as a periodontitis-like disease, but instead a "dis-balance" of a foreign body response.

Etiology-Titanium particles

A foreign body reaction to the entire implant can occur, but other evidence suggests that small titanium particles around the implant can provoke an immune response as well. It has been proven that titanium ions can be found in the tissues surrounding both dental and orthopedic implants, which can result in tissue discoloration and foreign body reactions to these particles.[137, 149] The blood vessels in the nearby soft tissue and bone could allow these titanium particles to enter the blood stream and migrate to distant body organs. One study found that when dental implants were inserted into the mandibles of sheep, there was a slight increase in titanium found within the lungs and regional lymph nodes.[150] Two of these implants failed resulting in a much higher level of titanium in the lungs and lymph nodes (7-9.4 times the levels in controls). In the orthopedic literature, countless articles have discussed the issue of metal debris traveling to distant organs, often referred to as "metallosis."[147, 151] A study on human cadavers with joint replacements found that 68 percent of the patients had metallic wear particles in their lymph nodes near the aorta.[152] An additional 38 percent had metallic particles in their liver and/or spleen. These particles were found in aggregates surrounded by macrophages, which are cells that attempt to rid the body of debris. These particles were again more prevalent in patients that had a failed implant, which is similar to the findings in the sheep mandible study.

Titanium particles can be released from the implant surface in numerous ways. Titanium can simply dissipate from the implant surface during and after placement, it can flake off of the implant due to mechanical forces, and it can exfoliate due to oxidative corrosion of the implant surface. These titanium particles can vary in size from small ions to large titanium pieces.[152]

Whether titanium can exfoliate from the implant during surgical placement is a debatable topic. Most modern-day implants have a surface that is treated and roughened, which could facilitate the exfoliation of small pieces of titanium. Senna *et al.* inserted three different implant designs (Nobel, Straumann, and Astra) into bovine ribs in order

to evaluate the presence of loose titanium particles.[153] It was found that all three implant designs had a decrease in both surface area and surface roughness after insertion into bone. Loose titanium and aluminum particles were observed, mainly at the crestal portion of the bone. A separate study on the titanium plasma sprayed (TPS) implant surface found titanium granules in the soft tissue and bone after implant insertion.[154] Suarez *et al.* studied five different implant surfaces and found that the grit blasted surface resulted in the most titanium exfoliation during placement into bovine ribs.[155] Sridhar *et al.* simulated surgical placement of Straumann dental implants into foam blocks of varying densities designed to match different bone densities seen in the mouth.[50] The authors found that implant insertion does not result in exfoliation of titanium particles into the surrounding osteotomy site.

It is sometimes difficult to determine whether these titanium particles are exfoliated during or after implant placement. Studies have found titanium particles in the surrounding soft tissue after the implant has been in function. Olmedo *et al.* conducted exfoliative cytology of the peri-implant mucosa and found metal particles embedded in the soft tissue of both healthy and diseased implants.[156] The diseased implants displayed a higher concentration of metal within the soft tissue. Another study in Washington observed the plaque around healthy and diseased implants.[157] All implants displayed titanium particles within the plaque, but the diseased implants had significantly more titanium per unit area of plaque. These titanium particles could be from implant placement, metal fatigue, or simply dissolution of the titanium surface over time.

A phenomenon known as fretting corrosion occurs at the interface of two closely fitting surfaces when they are subjected to repeated micro-motion or vibration.[151] In the dental field, fretting corrosion can occur between the implant and the abutment that is attached to it.[158] Modern implant designs have attempted to minimize this micro-motion, but it is impossible to eliminate completely.[159] A very small gap between the implant and abutment, known as the microgap, allows for metal fatigue over time.

Fretting corrosion results in surface irregularities on both the implant and abutment and exfoliation of metal into the surrounding tissue. When metal-on-metal wear occurs,

the titanium oxide layer on the implant can be mechanically destroyed.[151] The implant will now be at risk for true oxidative corrosion so it is important for the implant to reform a titanium oxide layer. Tawse-Smith *et al.* took exfoliative cytology samples from the tissue of implants restored with zirconia abutments and crowns.[160] Elemental analysis revealed that high numbers of titanium particles were present at the implant abutment interface and in the soft tissue adjacent to the crown. Others found that when nonprecious metals are used for the abutment, the implant is at risk for a galvanic reaction between dissimilar metals resulting in corrosion and a loss of the titanium oxide layer.[161]

The original Brånemark implants were made of commercially pure titanium, while the modern implant is alloyed with other metals. Iron is added for corrosion resistance, aluminum is added for increased strength, and vanadium acts as an aluminum scavenger to prevent corrosion.[162] Steineman has shown that titanium alloys (TiAlV) are not as well integrated as pure titanium and have an enhanced corrosion rate.[145] According to Khan, titanium alloys have a better combination of corrosion and wear resistance, while pure titanium shows better corrosion resistance but inferior wear characteristics.[163] Modern titanium alloys are touted to be highly resistant to corrosion, but stress and wear can accelerate the corrosion rate of titanium.[24]

Continual loading, micro-motion, and acidic environments can result in permanent loss of the titanium oxide (TiO_2) film and eventual corrosion.[158] Oxidative corrosion involves losing metal due to a chemical reaction that takes place with an electrolyte or acid as the metal repassivates or reforms an oxide layer.[151] Tribocorrosion refers to the combination of both fretting corrosion and oxidative corrosion. With metals in general, this phenomenon can occur along the entire surface or only in select locations. Typically, the majority of the titanium implant is stable and only a select area that lost its TiO_2 layer will experience corrosion. This phenomenon is referred to as pitting corrosion since it forms small pits in the areas that experience corrosion. Olmedo *et al.* installed both sterile titanium implants and implants with pitting corrosion into rat tibiae.[164] The

implants with pitting corrosion displayed decreased bone-implant contact, and corrosion products were found within the bone.

The oral environment is completely different from the sterile environment where orthopedic implants are placed. Dental implants are constantly exposed to a variety of insults every day. If the implant is exposed to an acidic environment and if micro-motion is present, the implant is now susceptible to corrosion. The two known modalities in which an implant can be exposed to an acidic environment include acidic byproducts of oral bacteria and decontamination medicaments used by the dentist or patient.[165, 166]

It has been known for some time that normal metabolism of oral bacteria results in a release of lactic acid as a waste product. This can result in dental caries, gingivitis, periodontitis, or in this case, peri-implantitis. Sridhar *et al.* immersed sterile dental implants into either a bacterial medium or a control medium *in vitro*.[166] The bacteria created a sustained acidic environment leading to discoloration, deformation, corrosion, pitting, and rusting of the implant surface. In a follow-up study by the same authors, it was found that normal mechanical forces on the implant in combination with a bacterial medium resulted in accelerated corrosion and dissolution of metal ions.[159] These results were corroborated by a University of Washington study that found elevated levels of titanium within the plaque around implants with peri-implantitis when compared to the plaque around healthy implants.[157] An *in vitro* study in Italy exposed implants to healthy human saliva for incremental lengths of time.[167] Significant dissolution of metallic particles was seen as early as one week. Interestingly, trace amounts of vanadium were found at one day, which questions the stability of the TiAlV alloy used in modern implants.

Another potential mechanism for corrosion is acidic medicaments used to decontaminate the implant surface. Wheelis *et al.* conducted an *in vitro* study to evaluate the corrosive effects of several detoxification solutions on Ti and TiAlV dental implants.[165] The solutions included citric acid, hydrogen peroxide, chlorhexidine gluconate, tetracycline, doxycycline, sodium fluoride, peroxyacetic acid, and treatment with a CO_2 laser. The treatments consisted of either immersing the implant in the

solution or rubbing the implant with a cotton swab soaked in solution. Implants that were immersed in a solution with a pH less than three displayed corrosion and pitting of the implant surface. The authors also noted a change in color of the acidic solutions, which suggests that titanium exfoliated from the implant. When rubbing was used, any solution with a pH less than 5.5 caused significant discoloration and pitting. Evaluation of the cotton swabs after they were used displayed remnants of titanium. With the immersion protocol, commercially pure Ti displayed less corrosion compared to the TiAlV alloy. These results suggest that when decontaminating an implant surface, the safest treatments include sodium fluoride, three percent hydrogen peroxide, and treatment with a CO_2 laser. Chlorhexidine can be applied to the implant surface, but if it is burnished with a cotton swab, corrosion is possible.

There is evidence that implant surface delamination can occur as well. Delamination refers to exfoliation or cleavage of a portion of the implant surface resulting in a large titanium particle in the vicinity and exposure of the underlying implant body. Rodrigues *et al.* have found corrosion in conjunction with surface delamination in both orthopedic and dental implants.[158, 168] Delamination of dental implants can be caused by micro-motion in an acidic environment resulting in exposure of the inner titanium body and accelerated dissolution.[158] After implant surface delamination, the underlying titanium body is unable to form a titanium oxide layer if it is not exposed to oxygen. This results in a highly reactive surface that will interact with nearby acids and electrolytes in order to stabilize. Sridhar *et al.* found that cyclic occlusal forces may result in surface delamination as well, which corresponds with the concepts of micro-motion and fretting corrosion.[159]

Based on the present data, there are several avenues that can lead to corrosion of titanium dental implants. To the best of the author's knowledge, there is insufficient evidence to say whether a corroded implant surface can be maintained in health. However, there is emerging evidence that suggests foreign particles embedded in the tissue can provoke an inflammatory response. A study on orthopedic implants demonstrated that metal debris can trigger inflammation *in vivo*.[169] Wilson *et al.*

obtained soft tissue biopsies around dental implants with peri-implantitis and evaluated them with light microscopy and SEM.[49] Titanium and/or dental cement were found in 34 of 36 biopsies and were surrounded by plasma cells, giant cells, and other inflammatory cells. Another study demonstrated that titanium debris can trigger a DNA damage response in oral epithelial cells.[155] These studies suggest that foreign debris around titanium implants is not well tolerated.

The aims of the present investigation are: (1) to evaluate the presence of foreign particles found in proximity to failing dental implants that have been removed; (2) to examine the effect that these foreign particles have on the surrounding tissues. Light microscopy, SEM (scanning electron microscopy), and EDS (energy-dispersive x-ray spectroscopy) methods will be employed.

2. MATERIALS AND METHODS

Patient Enrollment

The Institutional Review Board of Texas A&M University College of Dentistry (TAMUCOD), Dallas, Texas, reviewed and approved the protocol for this prospective, cross-sectional *ex vivo* study. A total of 21 patients (8 males, 13 females, aged 26 to 78 years; mean age: 61.4) possessing 34 dental implants were enrolled between May 2016 and November 2017. One female patient never returned for implant removal resulting in a total of 20 patients and 33 extracted implants. Additionally, one new implant (NobelReplace 4.3x11.5 mm CC RP) was taken directly out of the factory packaging and served as a negative control. Medical history, smoking status, gender, age, and location of implant were recorded for each patient. Patients were enrolled when the treating clinician deemed the implant as either failing or non-restorable. Early failures were defined as implants that failed before or at time of abutment connection.[170] Late failures were defined as implants with bleeding upon probing and/or suppuration upon probing with at least 50 % radiographic bone loss, which is a variation of previous definitions.[43, 44] Positive controls were defined as implants that met the criteria for implant success proposed by Albrektsson *et al*.[31] These criteria include immobility of the implant; lack of peri-implant radiolucency; < 0.2 mm vertical bone loss after the first year of service; and absence of pain, infection, neuropathy, paresthesia, or violation of the mandibular canal. These were obtained when the implant was either non-restorable or in a location that may affect patient health. Participants were recruited using the convenience sampling method in order to maximize the sample size. Patients were excluded if they had any condition that contraindicated surgery, including poorly controlled systemic conditions, immunosuppressive medications, and pregnancy.

Clinical Protocol

Four implants were removed in a private practice setting by Dr. Tom Wilson. All other implants were removed by residents with faculty supervision in the Departments of Graduate Periodontics and Graduate Oral and Maxillofacial Surgery. Standard surgical protocol was used to remove the implants, including reverse torque devices, trephine burs, and surgical burs as needed. The remaining sockets were debrided of any inflammatory tissue and augmented with a bone graft when indicated. Appropriate antibiotics were prescribed as needed and the patient was given the option to replace the implant when feasible. The extracted implant and any discarded tissues were immediately placed into 37 % neutral buffered formalin or type II collagenase/dispase enzymatic medium.

Group Allocation and Laboratory Analysis

A total of 34 implants (28 failed, 5 positive control, and 1 negative control) were examined. Six implants (5 failed and 1 positive control) were assigned to group E, which was an exploratory investigation using enzymatic degradation of the peri-implant tissues. All remaining implants were allocated into group GS (23 failed, 4 positive controls, and 1 negative control), which entailed histologic, SEM and EDS analysis of ultrathin ground sections.

Group E was designed for direct identification of any foreign particles embedded in the peri-implant tissues. These specimens were placed into type II collagenase/dispase and incubated at 37 degrees Celsius for 24 hours in order to enzymatically digest the tissues surrounding the implant. The implant was removed and the remaining medium was centrifuged at 2200 rpm for 15 minutes. The supernatant containing collagenase/dispase was removed using a pipette and the remaining 500 μL sample was smeared onto a glass slide and allowed to air-dry. This slide was then sputter-coated with gold for thirty seconds and imaged using a Jeol JSM-6010LA scanning electron

microscope. The observation conditions were metals, conductive, and the EDS detector was on. The map EDS function was used for elemental analysis throughout the slide. Any radiopaque areas were further analyzed with point EDS. The map function gives a general overview of the elements present throughout the specimen while point EDS gives the specific elements found for each point that is selected on the specimen.

Group GS underwent ground section preparation prior to imaging. These specimens were dehydrated using a series of ethanol baths (50 %, 70 %, 95 %, 100 %, and 50/50 mix of 100 % ethanol and 30 % Technovit), embedded in 100 % Technovit 7200 glycol methacrylate, and sectioned longitudinally into three or four sections using an Exakt diamond band saw. An Exakt grinding machine was used to grind these sections to a thickness of approximately 100 μm. All sections were photographed using a Leica light microscope prior to further analysis.

Representative histologic sections were stained using 1 % toluidine blue, rinsed with 70 % ethanol, and mounted using xylene-based mounting medium. They were then imaged using light and bright-field microscopy at 3x, 10x, 20x, 40x, and 100x magnification. The remaining sections were sputter-coated in gold for one minute and then examined and imaged using SEM at 30x, 180x, 750x, 1200x, 2200x, 3300x, and 5500x. Any areas that displayed foreign debris or bacteria were further analyzed using point EDS. Several areas that appeared to have normal bone to implant contact were also imaged and evaluated with EDS for comparison.

3. RESULTS

Group E

A total of 6 implants (5 failed and 1 positive control) were available for enzymatic digestion of the peri-implant hard and soft tissues. A representative sample with elemental analysis is displayed in Figure 1. All samples contained carbon, oxygen, and nitrogen, the primary elements in organic matter. Calcium and phosphorus were found in trace amounts (mean mass % of 4.9 and 1.9, respectively). Sodium and chloride were found in small amounts (9.28 % and 8.30 %, respectively). Silicon ranged from 0 % to 16.8 % (mean: 7.9 %) and zinc ranged from 0 % to 12.2 % (mean: 4.3 %). Zinc was not found in any of the control samples and titanium was not found in any of the failed or control samples.

Group GS

A total of 28 implants (23 failed, 4 positive controls, and 1 negative control) were evaluated using light microscopy and SEM. Figure 2 displays unstained light microscopy slides with titanium particles in the vicinity of all failing and positive control specimens. Compared to controls, the failed implants displayed a greater number and size of titanium particles (>10 μm in any dimension). These particles had a black color that matched the color of the titanium implant itself. In some failing implants, the shape of the implant surface was altered in the same area that this titanium exfoliation occurred. Larger particles could occasionally be matched to the implant surface from which it exfoliated. The positive controls displayed small and scarce (<10 particles at 100x magnification) foreign particles with no apparent alteration to the implant surface. The negative control (factory implant) revealed scarce, small artifacts that were far from the implant surface and did not match the color of titanium.

Stained slides, in Figure 3, revealed better contrast between the titanium particles and the surrounding tissues. Titanium particles were commonly observed in proximity to soft tissue, connective tissue, and bone undergoing osteolysis. Inflammatory cells such as PMNs and lymphocytes were observed. Titanium particles were less frequently seen in the vicinity of bone that appeared healthy. The positive control specimens displayed a smaller number of titanium particles and a greater presence of healthy bone surrounding the implant surface. However, titanium particles were found near the lumen of intrabony blood vessels for both failed and control implants.

Delamination of the implant surface was observed in failed implants (Figure 4). Surface delamination was associated with the presence of inflammatory cells and numerous titanium particles. None of the control specimens displayed this phenomenon.

Bacterial cocci and bacilli were seen in the vicinity of failed implant specimens, portrayed in Figure 5. These colonies were always associated with titanium particles. Bacterial colonies were not found in any of the control specimens.

SEM analysis of group GS revealed countless particles that could be verified as titanium using EDS. These particles were found in the vicinity of the external implant surface as well as in the screw access hole (Figure 6). 490 individual points (415 failed, 30 positive control, 45 negative control) were selected and evaluated using EDS. Points that were not connected with the implant body were further evaluated. 252 points near failed implants and 8 points near positive control implants contained titanium. The titanium points had a mass percent range from 1.26 % to 100 % (mean: 38.18 %). Titanium points found near positive controls were within the bone-implant interface and were not visibly seen. The negative control implant displayed occasional debris in the vicinity. EDS analysis revealed that none of this debris was made up of titanium and was simply artifact. Figure 7 displays a fractured implant that had bacterial cocci growing into and around the fracture. Point EDS reveals the presence of titanium within these bacterial colonies.

4. DISCUSSION AND CONCLUSIONS

Group E entailed a laboratory method that, to the author's knowledge, has never been used on peri-implant tissues. The lack of titanium particles found within these specimens may be due to methodical error since titanium particles were found in all specimens of group GS. The very small sample size in group E may have also influenced these results. Calcium and phosphorus, detected by EDS, were related to the presence of bone minerals. Sodium and chloride were most likely present due to the use of saline during implant removal and processing. Since glass slides contain silicon, any detection of silicon was considered part of the glass slide and not dental cement. However, zinc was present in select specimens and is not a component of glass slides. This suggests that the detection of zinc may be due to the presence of dental cement within the samples.

Burbano *et al.* conducted SEM of soft tissue biopsies taken from implants with cement-retained crowns and peri-implantitis.[51] The elements found in five different commercially available cements were identifiable in all 19 specimens. These elements were silicon, aluminum, zirconium, and zinc. Zinc is present in cements containing zinc oxide eugenol (TempoCem), zinc phosphate (Fleck's), and zinc oxide noneugenol (Temp-Bond). Wilson found cement in 34 of 42 peri-implantitis biopsies.[48] The majority of these implants were restored to health after removal of excess cement. Since zinc was found in certain group E specimens, it is plausible that this was due to the presence of cement.

All failed and positive control implants in group GS had titanium particles present in the vicinity to varying extents. A greater number of titanium particles were present near failed implants than controls, which may be due to corrosion-induced titanium exfoliation which has been suggested in previous studies.[49, 157, 158] Some authors found that titanium exfoliates during implant placement and others found that it does not.[50, 153, 155] It is possible that the present specimens experienced titanium exfoliation during placement and/or removal. However, this does not account for the fact that a

much greater number and size of titanium particles were associated with failed implants when compared to positive controls. Another possible dispute is that the process of grinding these specimens resulted in titanium exfoliation. The fact that there was no titanium exfoliated from the negative control (factory implant), which underwent the same grinding process, supports the argument that titanium is not exfoliated during processing.

Titanium particles were present within the lumen of regional blood vessels in both failed and positive control implants, which may be cause for concern. Studies in both dental and orthopedic literature have found titanium particles in the lungs, regional lymph nodes, liver, and spleen.[150, 152] These studies found higher quantities of titanium in distant organs for those with failing implants. The only logical means for titanium to travel to distant organs is through the circulatory system. The present results suggest that a pathway exists for titanium particles to enter the circulatory system, and it is possible that a greater number of particles enter circulation when the implant is diseased.

The surface delamination found on failed implants corroborates the findings of several previous studies. Rodrigues *et al.* found corrosion in conjunction with surface delamination in failing orthopedic implants.[168] A separate study by Rodrigues *et al.* found that delamination of dental implants can be caused by micro-motion in an acidic environment resulting in exposure of the inner titanium body and accelerated dissolution.[158] The underlying titanium has not been exposed to oxygen and therefore never forms a titanium oxide layer. This results in a highly reactive surface that will react with nearby electrolytes. An *in vitro* study by Sridhar *et al.* found that cyclic occlusal forces result in surface delamination as well.[159] The results of the present study show that surface delamination is observed in an unhealthy environment and is associated with a large number of titanium particles.

Countless references validate that bacterial plaque is associated with peri-implantitis and implant failure.[41, 90, 91] The microbiota typically associated with peri-implantitis are similar to those seen with periodontitis, namely, gram negative anaerobic rods, fusobacteria, and spirochetes.[90] Interestingly, cocci were seen in one fractured

implant under SEM, which is a bacterium typically associated with health. A gram stain may have aided in identifying the bacterial characteristics. Regardless, the fact that these cocci were found in the body of the implant, as opposed to a healthy peri-implant sulcus, clearly demonstrates the lack of health for this particular specimen.

All bacterial colonies found in this study were associated with titanium particles. This validates a study by Safioti *et al.* which found higher levels of titanium in plaque samples taken from implants with peri-implantitis when compared to healthy controls.[157] Another study found that bacterially produced lactic acid results in corrosion and release of metal particles from the implant surface.[166] There is mounting evidence that bacteria affects not only the peri-implant tissues, but the actual implant body as well. This could result in an environment that is very difficult if not impossible to repair by contemporary peri-implantitis treatment modalities.

Conclusions

A greater number and size of titanium particles were found in the vicinity of failed implants when compared to healthy controls. These titanium particles were associated with bacterial plaque, delamination of the implant surface, and local vasculature. It is difficult to discern whether titanium particles are an initiating factor to implant failure or simply a result of other known etiologies. The findings in the present study suggest that corrosion of a titanium implant surface occurs *in vivo*. The resultant implant surface distortion and titanium exfoliation may produce an environment that is not compatible with health.

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APPENDIX

FIGURES

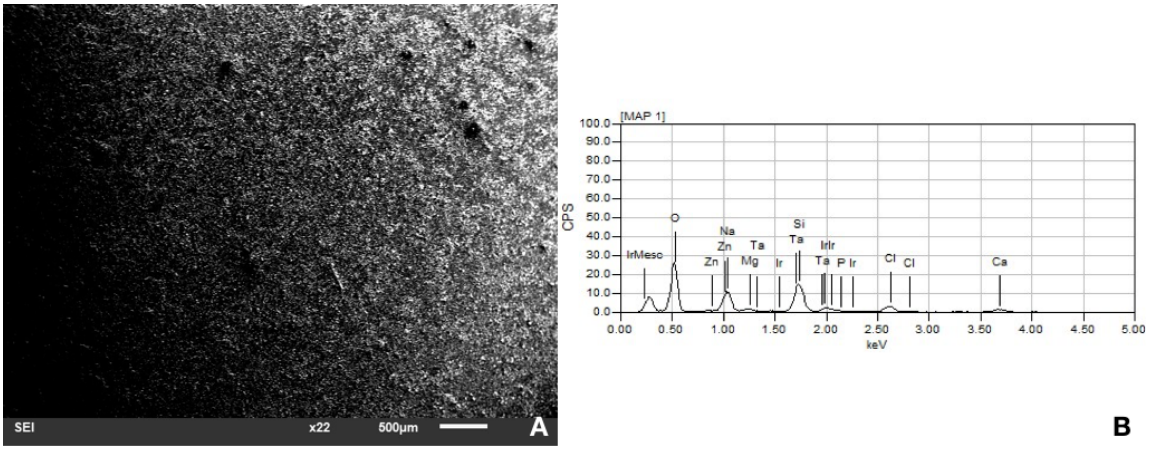


Figure 1. Representative specimen from Group E. A) Image taken with SEM at 22x magnification. B) EDS analysis portraying the presence of Zinc and Silicon.

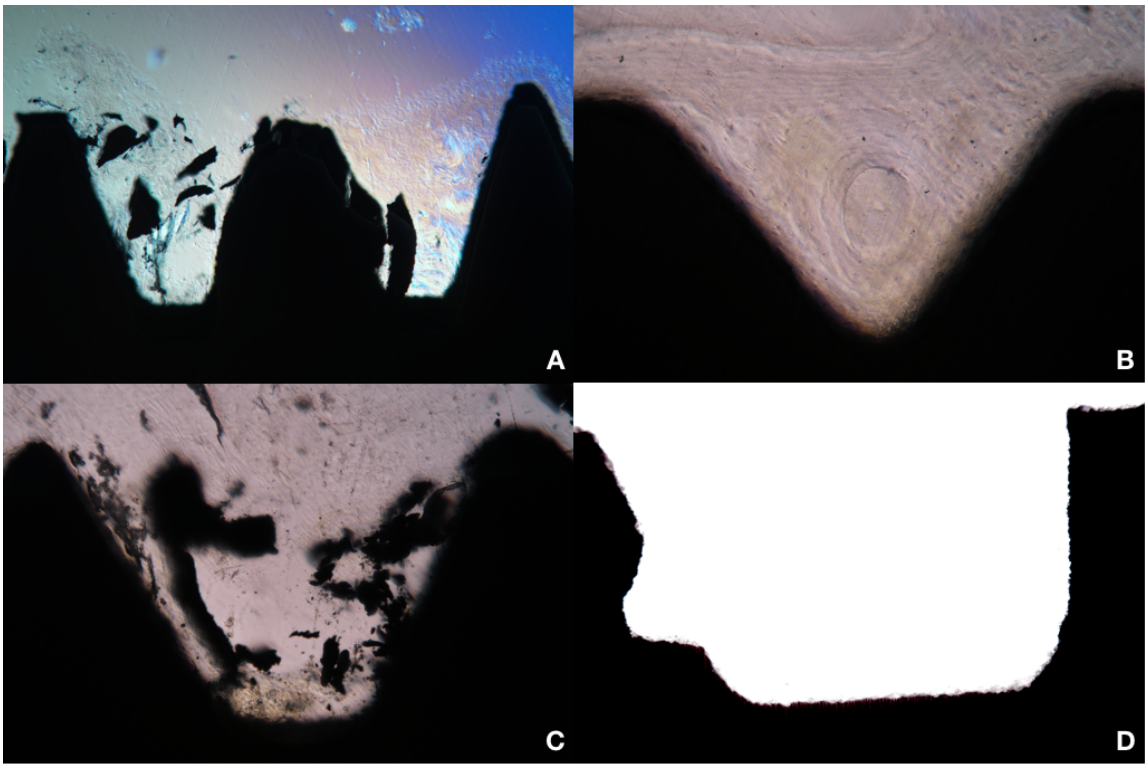


Figure 2. Unstained light microscopy depicting titanium particles in the vicinity of failed implants. A) Failed implant at 10X magnification with titanium debris. B) Positive control (healthy) implant at 20X. C) A failed implant at 20X with titanium debris. D) Negative control (factory) implant at 20x.

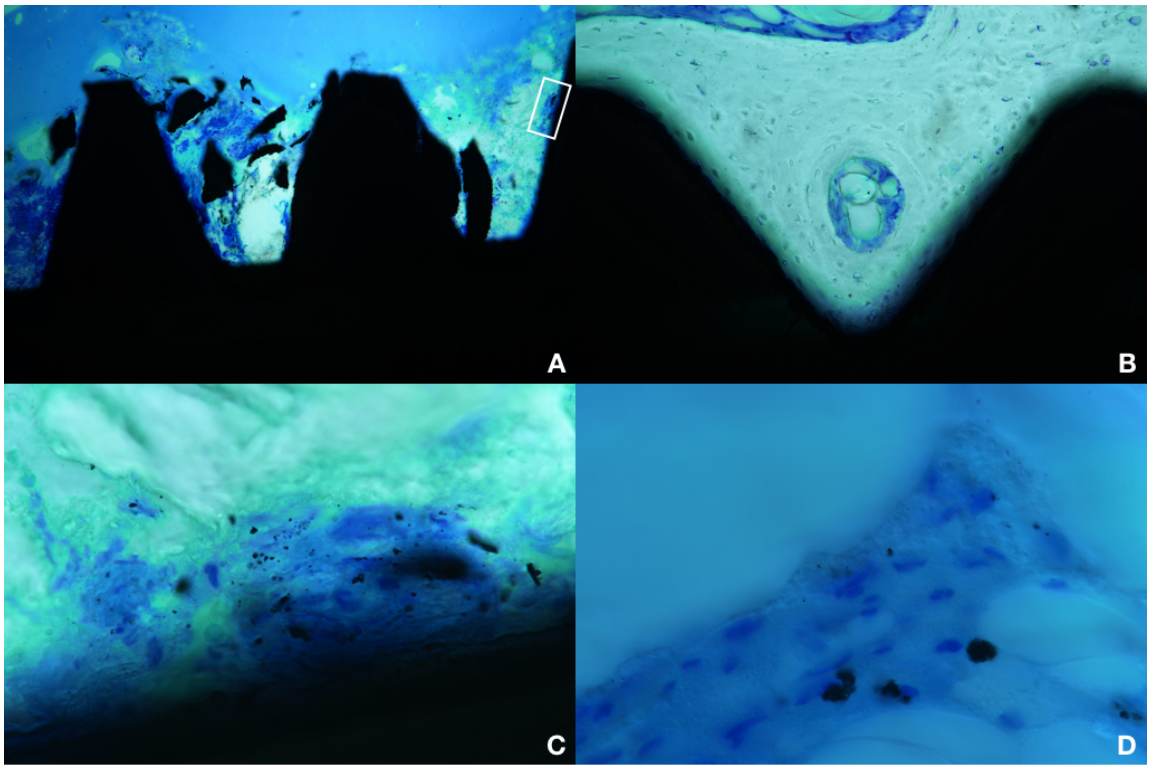


Figure 3. Stained light microscopy for histologic interpretation. A) Failed implant at 10x magnification with demineralized bone, connective tissue, and inflammatory cells. B) Positive control (healthy) implant at 20X. C) The same failed implant at 100X portraying the multitude of small titanium particles. D)The same control implant at 100X portraying the presence of small titanium particles in the vicinity of an arteriole.

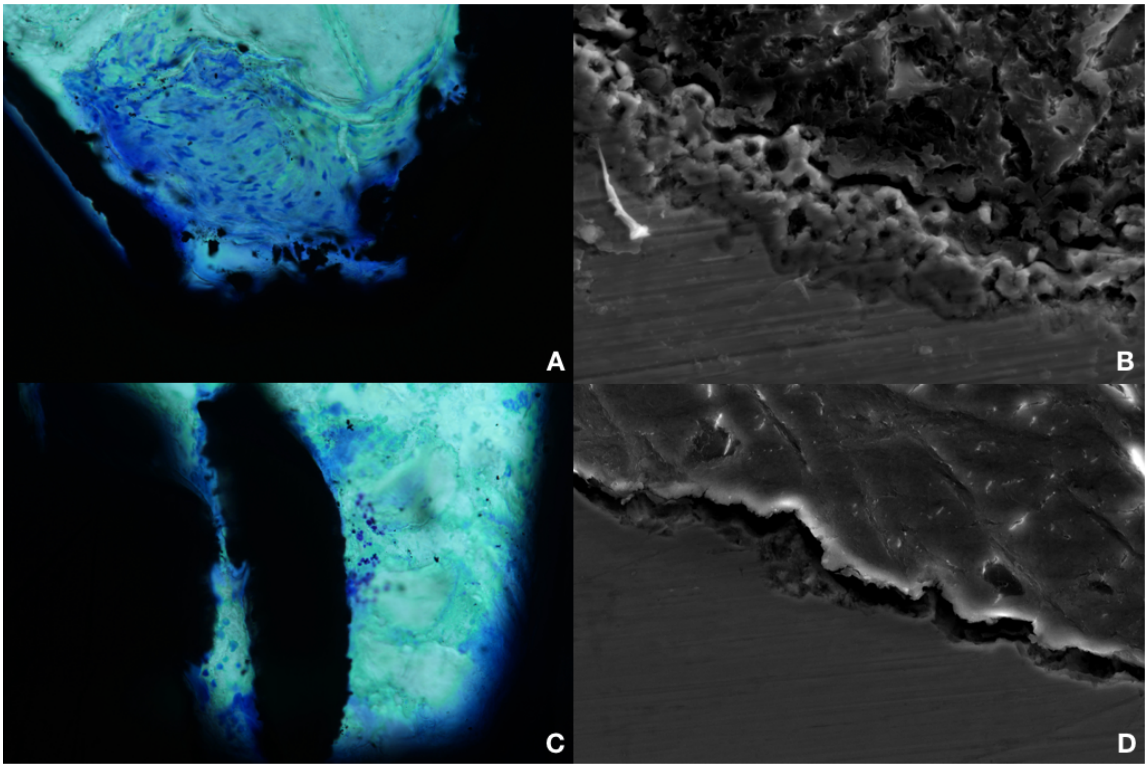


Figure 4. Delamination of the failed implant surface. A) Failed implant at 40X magnification showing complete delamination of the external implant surface. B) SEM of failed implant at 1200X with inflamed soft tissue and titanium particles. EDS of the soft tissue lining revealed the presence of Carbon, Oxygen, Phosphorus, and Titanium. C) A second implant at 40X with surface delamination. D) Positive control under SEM at 1200X with the lack of surface delamination and normal bone-implant interface.

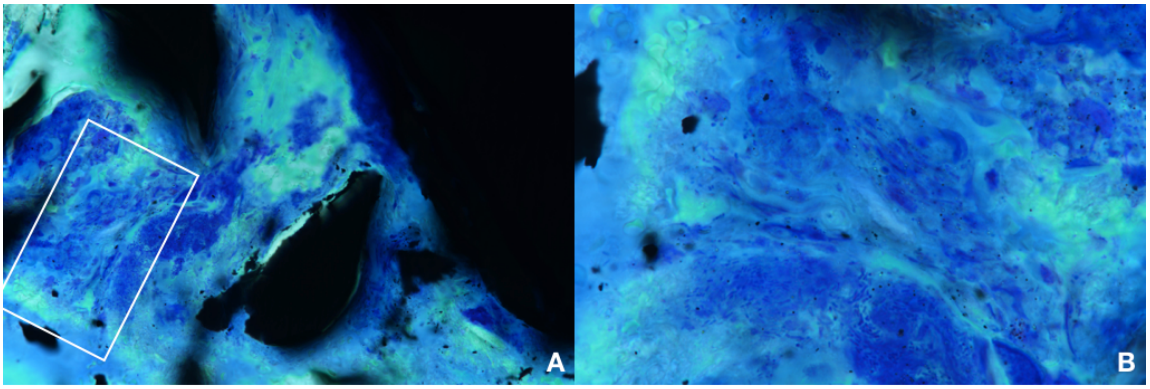
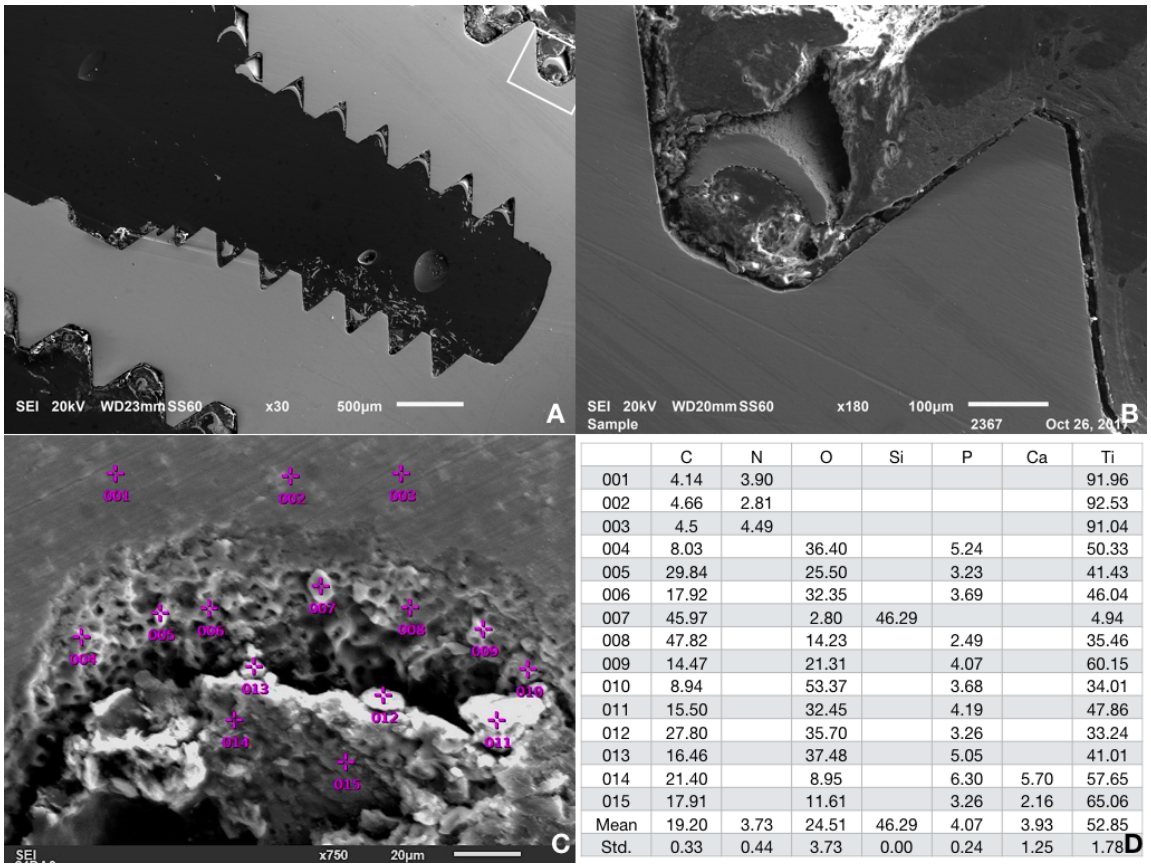


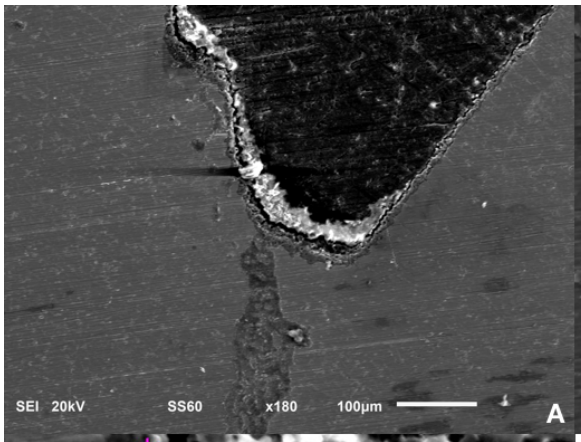
Figure 5. Failed implant depicting titanium particles within bacterial colonies. A) 40X magnification portraying countless bacilli and titanium particles. B) 100X of the same region. Note the presence of numerous small titanium particles and bacilli.

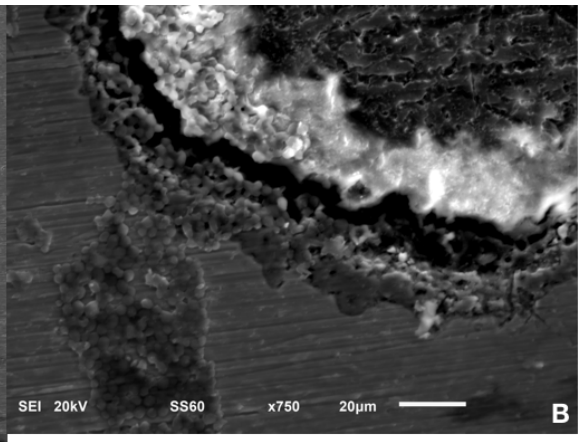


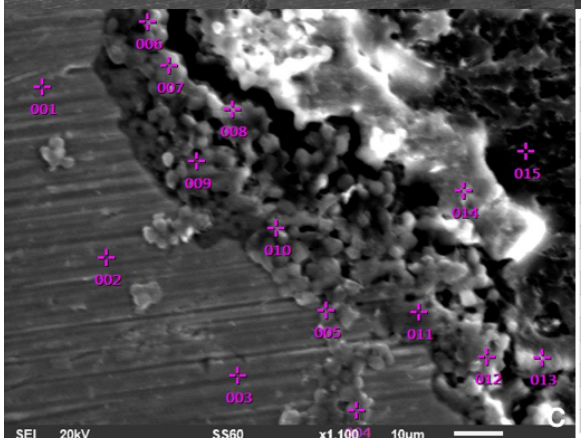
	C	N	O	Si	P	Ca	Ti
001	4.14	3.90					91.96
002	4.66	2.81					92.53
003	4.5	4.49					91.04
004	8.03		36.40		5.24		50.33
005	29.84		25.50		3.23		41.43
006	17.92		32.35		3.69		46.04
007	45.97		2.80	46.29			4.94
008	47.82		14.23		2.49		35.46
009	14.47		21.31		4.07		60.15
010	8.94		53.37		3.68		34.01
011	15.50		32.45		4.19		47.86
012	27.80		35.70		3.26		33.24
013	16.46		37.48		5.05		41.01
014	21.40		8.95		6.30	5.70	57.65
015	17.91		11.61		3.26	2.16	65.06
Mean	19.20	3.73	24.51	46.29	4.07	3.93	52.85
Std.	0.33	0.44	3.73	0.00	0.24	1.25	1.78

D

Figure 6. Titanium debris of varying sizes observed using SEM. A) 30X magnification of a failed implant possessing titanium debris within the internal screw connection and along the external implant surface. B) 180X of the same failed implant portraying a large titanium particle. C) 750X of a failed implant possessing small titanium particles embedded in the surrounding soft tissue. D) Point EDS showing the presence of titanium at all points. Point 7 is made up of 46.29 % silicon, which was considered artifact from the glass slide.







	C	N	O	P	Ca	Ti
001	5.28	3.54				91.18
002	4.85	3.59				91.56
003	4.78	3.84				91.38
004	26.70	4.78	10.47			58.05
005	32.22	9.76	17.17			40.85
006	49.86	15.02	20.17	2.38	1.20	11.37
007	47.07	9.29	22.04	3.72	2.50	15.38
008	64.95	14.17	15.29	1.44	1.20	2.95
009	9.18		33.19	6.03		51.6
010	30.12	8.41	26.44	4.77		30.26
011	7.13		32.17	6.49		54.21
012	46.12	13.45	22.44	2.32		15.67
013	64.29		19.45	3.83	4.16	8.27
014	27.50		38.52	14.09	19.89	0
015	100.00					0
Mean	34.67	8.58	23.40	5.01	5.79	37.52
Std. Dev.	16.87	1.54	4.56	3.03	6.30	7.12

D

Figure 7. A single failed implant that contains a micro fracture with the ingrowth of bacterial cocci. A) 180X magnification displaying the extent of the fracture and bacterial colonies. B) 750X magnification highlights a well-organized bacterial colony that has infiltrated the implant surface. C) EDS analysis of these same bacteria at 1100X. D) Results of EDS reveal the presence of titanium within the bacteria. Points 14 and 15 are the only areas with undetectable levels of titanium.