On dental implant failure and patient-related factors

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UNIVERSITY OF GOTHENBURG
Gothenburg 2021
To my family
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ABSTRACT

Dental implants function as anchorage for dental prostheses. In a small number of cases, osseointegration fails to establish or be maintained around the implants, but the reasons for these failures are not yet fully understood. This thesis investigated a cohort of patients rehabilitated with dental implants, with respect to incidence of implant failure and potential risk factors for early implant failure, and explored the gene expression of selected biological markers in peri-implant bone sites with severe bone loss.

Patient data were retrospectively compiled from one specialist referral clinic. Data were analyzed on the patient level covering 27-31 years of implant treatment (Studies I, II and III). Study I described the incidence of implant failure for the total group of rehabilitated patients. In Studies II and III, multivariable logistic regression analyses of several anamnestic and clinical variables were performed to find potential risk factors for early implant failure in edentulous jaws. In Study IV, an experimental pilot study, gene expression analysis was performed in biopsies from bone and peri-implant crevicular fluid (PICF) surrounding implants with severe bone loss compared to un-affected bone, using qPCR technique.

In Study I, a total number of 39,077 implants were inserted in 8528 patients. Of these, 9% of the rehabilitated jaws were registered with implant failure and 69% of these had the first implant failure during the first year of function. Implant failures were more frequent in the maxilla as compared to the mandible. The change from implants with turned, minimally rough surfaces to implants with different moderately rough surfaces coincided with a decrease of early implant failure. In Study II, the incidence of early implant failure in edentulous jaws was higher in the maxilla compared to the mandible, with turned as well as moderately rough surfaces. The highest risk of early implant
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In Study I, a total number of 39,077 implants were inserted in 8528 patients. Of these, 9% of the rehabilitated jaws were registered with implant failure and 69% of these had the first implant failure during the first year of function. Implant failures were more frequent in the maxilla as compared to the mandible. The change from implants with turned, minimally rough surfaces to implants with different moderately rough surfaces coincided with a decrease of early implant failure. In Study II, the incidence of early implant failure in edentulous jaws was higher in the maxilla compared to the mandible, with turned as well as moderately rough surfaces. The highest risk of early implant
failure was related to the maxilla together with implants with a turned surface. Older age at implant surgery was associated with lower risk of early implant failure. In Study III, nine risk factors for early implant failure were identified: systemic disease, allergies, food allergies, smoking, analgetic medication, implants in the opposing jaw, low primary stability, reduced bone volume, and healing complications. In Study IV, an upregulation of pro-inflammatory cytokines and bone degradation markers were found in bone biopsies from bone loss sites compared to biopsies from unaffected bone in the same patients. The results were partly corresponded by the PICF samples. The results need to be interpreted with caution due to the small sample size and the pilot study design.

In conclusion, implant failures occurred in 9% of the jaws. Several risk factors for early implant failure were identified, which need to be considered in future implant rehabilitations. There was a difference in the gene expression around implants with severe bone loss compared to samples from un-affected bone. Further studies are needed to describe the processes associated with implants that display ongoing bone loss.

**Keywords**: early implant failure, patient factors, multivariable logistic regression analysis, gene expression analysis


Information om patienter med implantatförlust insamlades retrospektivt och täckte en behandlingsperiod om 27–31 år (Studierna I, II och III). Studie I redovisade incidensen av implantatförlust för hela gruppen, medan studierna II och II utredde ett stort antal potentiella riskfaktorer för tidig implantatförlust i helt tandlösa käkar med multivariabel logistisk regressionsanalys. I Studie IV, en experimentell pilotstudie, undersökt genuttrycket i biopsier från peri-implantärt ben och tandköttsvätska (PICF) vid implantat som uppråt omfattande benförlust jämfört med prov från opåverkat ben, med användande av qPCR-teknik.

Studie I inkluderade 39 077 implantat i 8528 patienter. Implantatförlust registrerades i 9% av de rehabiliterade käkarna, varav 69% inträffade under första året i funktion. Implantatförlust var mer frekvent i överkäke jämfört med underkäke, och i samband med skiftet från implantat med svarvad, minimalt rå yta mot implantat med moderat rå yta minskade förekomsten av tidiga implantatförluster. I Studie II konstaterades att risken för tidig implantatförlust var relaterad till typ av käke, typ av implantatyta och patientens ålder vid implantatinstallationen. Tidig implantatförlust förekom oftare i överkäke än underkäke, och äldre ålder vid implantatinstallation var relaterat till högre risk för tidig implantatförlust. I Studie III kunde nio riskfaktorer identifieras relaterade till tidig implantatförlust i helt tandlösa käke: systemisk sjukdom, allergier, matallergier, rökning, smärtstillande medicinering, implantat i motstående käke, låg primärstabilitet, reducerad benvolym samt läkningskomplikationer. I Studie IV redovisades ett uppreglerat uttryck av pro-inflammatoriska cytokiner och benresorptionsmarkörer i ben från implantatnära biopsier jämfört med biopsier från opåverkat ben i samma patienter. Prover från PICF visade på delvis liknande uttryck av förhöjda nivåer av proinflammatoriska markörer. Resultatet bör tolkas med försiktighet eftersom analyserna utförts i en liten patientgrupp och med ny metodik.

This thesis is based on the following studies, referred to in the text by their Roman numerals.


IV. Malm MO, Jemt T, Trindade R, Stenport V. Gene expression in bone around dental implants with severe bone loss: An experimental pilot study with human biopsies. In manuscript.

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LIST OF STUDIES

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## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ARG1</td>
<td>Arginase-1</td>
</tr>
<tr>
<td>BMP-2</td>
<td>Bone morphogenetic protein</td>
</tr>
<tr>
<td>c.p.</td>
<td>Commercially pure</td>
</tr>
<tr>
<td>CathK/CTSK</td>
<td>Cathepsin K</td>
</tr>
<tr>
<td>DKK-1</td>
<td>Dickkopf-related protein-1</td>
</tr>
<tr>
<td>FBGC</td>
<td>Foreign body giant cell</td>
</tr>
<tr>
<td>IL-10</td>
<td>Interleukin 10</td>
</tr>
<tr>
<td>IL-13</td>
<td>Interleukin 13</td>
</tr>
<tr>
<td>IL-17</td>
<td>Interleukin 17</td>
</tr>
<tr>
<td>IL-1β</td>
<td>Interleukin 1 beta</td>
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<td>Interleukin 4</td>
</tr>
<tr>
<td>IL-8</td>
<td>Interleukin 8</td>
</tr>
<tr>
<td>ISQ</td>
<td>Implant Stability Quotient</td>
</tr>
<tr>
<td>M-CSF</td>
<td>Macrophage colony-stimulating factor</td>
</tr>
<tr>
<td>MMP-8</td>
<td>Matrix metalloproteinase 8</td>
</tr>
<tr>
<td>MMP-9</td>
<td>Matrix metalloproteinase 9</td>
</tr>
<tr>
<td>MR</td>
<td>Moderately rough (implant surfaces)</td>
</tr>
<tr>
<td>NE</td>
<td>Neutrophil elastase</td>
</tr>
<tr>
<td>OC</td>
<td>Osteocalcin</td>
</tr>
<tr>
<td>OPG</td>
<td>Osteoprotegerin</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PGLYRP-1</td>
<td>Peptidoglycan recognition protein-1</td>
</tr>
<tr>
<td>PICF</td>
<td>Peri-implant crevicular fluid</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>qPCR</td>
<td>Quantitative real-time polymerase chain reaction</td>
</tr>
<tr>
<td>RANKL</td>
<td>Receptor activator of the NFκB-ligand</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>RFA</td>
<td>Resonance Frequency Analysis</td>
</tr>
<tr>
<td>SOST</td>
<td>Sclerostosis</td>
</tr>
<tr>
<td>SSRI</td>
<td>Serotonin selective re-uptake inhibitor</td>
</tr>
<tr>
<td>T</td>
<td>Turned (implant surfaces)</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>Tissue inhibitor of matrix metalloproteinase</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumor necrosis factor alpha</td>
</tr>
<tr>
<td>TRAP</td>
<td>Tartrate resistant acid phosphatase</td>
</tr>
<tr>
<td>TREM-1</td>
<td>Triggering receptor expressed on myeloid cells -1</td>
</tr>
</tbody>
</table>
INTRODUCTION

For more than 50 years, dental implants have offered a reliable method for anchorage of dental prostheses in the rehabilitation of edentulous patients, providing millions of people worldwide improved oral function and renewed self-esteem. Success and survival of the implants are high, but a few percent of the patients exhibit bone loss or failure of the osseointegration of the implants, with a subsequent risk to lose the anchorage of their prosthesis. Because this failure can cause problematic situations for the individual patients, the survival of the implants is of utmost importance. Although the understanding of reasons related to failure of dental implants is constantly growing, more knowledge is needed that will help predict the conditions that lead to implant failure, information that can be used in order to design strategies and techniques to prevent implant failure.

1.1 IN RETROSPECT

Since the 1960s, titanium implants have been developed to be used as anchorage for dental, craniofacial and orthopedic prostheses in thousands of people all over the world. Before the discovery of bone growth in close vicinity to the titanium surface, later termed osseointegration of titanium implants, dentists had been rehabilitating patients with different types of implants, without bone anchorage, with low success rates and subsequent discomfort for the patients (e.g., sub-periosteal implants, blade implants and core-vent-implants).

In the late 1970s, the osseointegration concept for the dental application was recognized in the dental community in Sweden, and in 1982 it gained approval from the international counterpart. In the beginning, the osseointegrated implants were made of commercially pure (c.p.) titanium with a machined, turned surface with a minimally rough surface. Further development of the material included the inclusion of other components in the alloy (e.g., small amounts of nitrogen, oxygen and iron) to increase mechanical strength. The c.p. titanium of grade IV is most commonly used for the dental application today. The implant surfaces have been modified over the years to improve the bone healing, including various additive or subtractive methods such as blasting or coating, oxidization, and etching procedures. Rough surfaces (Sa>2.0µm) have been tested but demonstrated increased bone loss, and therefore are not used today. Today, most commercially available implants have moderately rough surfaces.
1 INTRODUCTION

For more than 50 years, dental implants have offered a reliable method for anchorage of dental prostheses in the rehabilitation of edentulous patients,\textsuperscript{1-3} providing millions of people worldwide improved oral function and renewed self-esteem.\textsuperscript{4} Success and survival of the implants are high, but a few percent of the patients exhibit bone loss or failure of the osseointegration of the implants, with a subsequent risk to lose the anchorage of their prosthesis.\textsuperscript{5} Because this failure can cause problematic situations for the individual patients, the survival of the implants is of utmost importance. Although the understanding of reasons related to failure of dental implants is constantly growing, more knowledge is needed that will help predict the conditions that lead to implant failure, information that can be used in order to design strategies and techniques to prevent implant failure.

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dimensions of implants (width and length) are readily available for selection depending on the available bone volume and the location in the jaws, as well as different macro-geometries designed for different bone qualities. New alloys, such as titanium-aluminum-vanadium (Ti6Al4V) as well as titanium-zirconia (TiZr), have been developed with higher mechanical strength to enable smaller dimensions of the implants. In addition, ceramic implants made from zirconium-dioxide, (ZrO2) are commercially available, offering a metal-free alternative.

1.2 EDENTULOUSNESS

Teeth can be lost for various reasons. Dental caries and periodontal disease are the most common reasons for tooth loss, but also trauma, fractures, and different lesions in the jaws can result in missing teeth, as well as tooth absence due to agenesis. For most people, being completely edentulous leads to an inability to function and social stigma.

Complete edentulism is generally the result of severe dental disease, which may be correlated to general health, behavior, education, and income. Prevalence of complete edentulism has been decreasing throughout the world, but remains a health issue. In 2010, the global prevalence rate of complete edentulism was reported to be 2.3%, and in Sweden, the prevalence has been consistently declining to numbers ranging from 0.3%-0.7% to 2.3%.

Tooth loss has been associated with different physiological conditions (i.e., systemic diseases). However, the presence of comorbid disease does not describe any causal relationship between tooth loss and other diseases. For example, whether edentulism causes malnutrition - or vice versa - remains to be understood. Moreover, confounding factors such as smoking, and social status must also be acknowledged, as both are related to health conditions and tooth loss. A recent study from a Swedish cohort found that being born outside of Sweden, single living, not feeling healthy, and smoking predicted reduced number of teeth. Furthermore, the comorbidity between edentulism and obesity, cardiovascular disease, and diabetes as well as immunological diseases such as rheumatoid arthritis (RA) has been demonstrated. Edentulism can be an independent predictor for cardiovascular mortality, which is also supported by findings within our group reporting that completely edentulous patients had a higher mortality than partially edentulous patients, and that the majority died from cardiovascular disease.
The age at which one becomes edentulous may also reflect on the general health status. The association between edentulism and angina pectoris was correlated with age, demonstrating higher prevalence in the younger age group.\(^2^6\) Compared to a reference population, edentulous patients in another younger age group (\(\leq 59\) years) had a significantly increased mortality due to cardiovascular diseases.\(^2^5\) Moreover, the findings were also correlated to the patients’ socio-economic status, where people with higher income and educational level had lower mortality than those with lower income and education.\(^2^5\) However, these correlations are complex and need to be studied further.

1.3 OSSEOINTEGRATION

1.3.1 IN GENERAL

The process that leads to the fixation of an inserted device in bone is called osseointegration, a term coined by Professor P-I Brånemark to describe the events occurring in the body, literally integrating the foreign material into bone tissue. The definition was originally “a direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant”.\(^2^7\) The phenomenon was simultaneously also studied by Schroeder et al.,\(^2^8, 2^9\) who were investigating the functional ankylosis of a hollow titanium cylinder in bone, without soft tissue encapsulation. The definition of osseointegration has been debated and refined, recently pushing the discussion towards describing the condition around an inserted implant in terms of a foreign body reaction, although this is still being debated.\(^3^0, 3^1\)

1.3.2 PROCESS OF OSSEOINTEGRATION

When a titanium implant is inserted into living bone tissue, a cascade of biological reactions occurs. Immunological activation starts immediately as the body tries to heal the damaged bone. Bone healing around an implant can be divided into three phases: inflammation, bone regeneration, and bone remodeling. The healing process in bone has been resembled to intramembranous bone healing with direct bone formation,\(^4, 9\) as the titanium is surrounded by living bone tissue. This description assumes, however, that the titanium is inert and that the bone healing encapsulates the implant as if it were not there.\(^4\) Recent studies demonstrate that titanium is most likely not
inert, but activates the immune system at an early stage after insertion, resulting in the encapsulation of bone,\(^3^2\) which was suggested earlier.\(^3^0\) Moreover, it has been suggested that early events in the bone healing process determines whether osseointegration will be successful, and several factors may influence the outcome of this process (e.g., the physical properties of the implant as well as the cell response, the vascularization in bone and interaction with oral microflora.\(^4,3^0,3^3,3^4\) Bone formation around a titanium implant can be described as a combination of osteoinduction, or contact osteogenesis, (i.e., the stimulation of cell development to induce bone formation directly on the implant surface), and osteoconduction, or distance osteogenesis (i.e., bone growth towards the implant surface, which eventually contacts the implant surface).\(^3^5,3^6\)

### 1.3.2.1 MOLECULAR EVENTS

Following the surgical insertion trauma, proteins are immediately adsorbed on the implant surface, and this is followed by cell recruitment and differentiation. This protein matrix with high affinity to the implant surface affects how the osseointegration develops, as the protein matrix acts as a bridge between the cells and the surface.\(^3^3\) Early in the blood clot formation, erythrocytes and platelets are found. Platelets are involved in the signaling of tissue damage by release of growth factors and cytokines that induce wound healing (e.g., platelet derived growth factor, PDGF, and transforming growth factor beta, TGF-ß),\(^4\) as well as complement system.\(^3^7\) This cascade of events induces chemotaxis of cells from blood and the surrounding endothelial and bone tissue, and the recruitment of cells to the area is determined by the release of several modulators that orchestrate the events. In the earliest stages, pro-inflammatory cytokines (e.g., TNF-α and IL-1ß) are released, which has been demonstrated in vivo and in humans.\(3^4,3^8,3^9\) Leukocytes are recruited and initially the polymorphnuclear (PMN) cell type neutrophils are predominating, but within 48 hours the macrophages predominate. These are led to the site by the influence of TNF-α and IL-1ß, as well as interleukin 8 (IL-8)\(^4,4^0\)

Mesenchymal stem cells (MSCs), are also found early in the healing process. MSCs, originating from the bone marrow, perivascular cells, and endosteum, differentiate into osteoprogenitors and osteoblasts, a process that is regulated by a complex series of growth factors, including bone morphogenetic proteins (BMPs) and the TGF-ß superfamily.\(^4^0,4^1\) The osteoblasts first produce an osteoid that serves as a collagenous matrix for bone before being further mineralized through the bone remodeling process, which is a process that reorganizes the bone tissue into mature bone, and involves both osteoclasts and
osteoblasts. Secreted by osteoblasts, osteocalcin (OC) can also serve as a marker for the late stages of mineralization during bone formation.

The remodeling process is highly regulated to balance the activity between the bone resorptive osteoclasts and the bone forming osteoblasts. The RANK/RANKL/OPG ratio has a key factor for this balance. RANK, a receptor on the osteoclast, is activated by binding to RANKL, which stimulates osteoclast activity. Osteoprotegerin (OPG) fine-tunes the osteoclastic activity by binding to RANKL, inhibiting further osteoclast stimulation. Several cells express RANKL, including osteoblasts and macrophages that have fused and become osteoclastic precursor cells. Furthermore, the remodeling of bone is regulated by various enzymes, e.g., macrophage colony stimulating factor (M-CSF), cathepsin K (Cath K), tartrate-resistant acid phosphatase (TRAP), and matrix metalloproteinases (MMPs).

### 1.3.2.2 CLINICAL EVALUATION OF DENTAL IMPLANTS

The absence of pain and immobility of the implant is considered necessary for successful bone formation around implants. Moreover, intraoral status of the peri-implant mucosa without swelling, suppuration and fistulas are generally needed for an implant to be considered clinically successful.

Radiographic imaging is a central diagnostic tool for evaluating implant integration with bone. Bone formation around the threads of the implant, without a radiolucent zone indicates osseointegration, whereas a radiolucent zone is considered to be related to a fibrous encapsulation. Furthermore, clinical stability can be tested with different methods (e.g., insertion torque measurements, resonance frequency analysis (RFA) and tactile perception and percussion test) to validate the support of bone and the stability of the implant both immediately after insertion as well as later in the life of the implant.

Clinical data demonstrate that dental implants can be inserted and integrated with bone tissue with reliable results. During the first decades of implant use, implants with a turned surface were inserted, with long-term survival exceeding 85%. Also, titanium-sprayed implants from the 1980s and 1990s display long-term survival rates of up to 88%. Over the last 20 years, most inserted implants have surface modifications, and long-term survival rates reach 83–100% for a number of different implant systems. Moderately rough anodically oxidized implants (TiUnite™, Nobel Biocare) demonstrated a one-year survival of 99.50% at the implant level and 99.12%
at the patient level, and ten-year survival rates of 95.14% and 91.50% on implant and patient level, respectively.\textsuperscript{58} Implants with TiO-blast\textsuperscript{TM} surface modification from AstraTech have been reported with an implant level survival rate of 95.5% after 12–15 years\textsuperscript{59} and 90% after ten years.\textsuperscript{60} In yet another long-term follow-up study of a commonly used implant system, (Straumann ITI implants) a 10-year survival rate of 98% (implant level) was reported.\textsuperscript{61} Several studies report that most of the implant failures occur within the first year after implant insertion, indicating the failure of bone formation after insertion.\textsuperscript{1, 62, 63}

1.3.3 FACTORS RELATED TO BONE FORMATION AROUND IMPLANTS

Bone healing around dental implants depends on several factors and can be regarded as a complex interplay between the host, surgical intervention, and material properties. After insertion, a homeostasis between these factors needs to be maintained in order to preserve the surrounding bone. When bone healing is impaired, the bone encapsulation of the implant is sometimes replaced by soft tissue encapsulation, which resembles a fibrous scar, with fibrous and sometimes epithelial downgrowth, or an immediate rejection.\textsuperscript{30, 33} Biomaterials science describes the series of events as a foreign body reaction, which in the final state of healing can be used to anchor prostheses to bone.\textsuperscript{33, 64, 65}

Patient related factors – e.g., general health issues and medications – can influence whether osseointegration is successful. For example, healing in general and bone healing in particular can be impaired by smoking, systemic inflammatory disease, and certain medications.\textsuperscript{66, 67}

1.3.3.1 IMPLANT CHARACTERISTICS

Titanium dioxide (TiO\textsubscript{2}) has properties that enable long lasting contact with living tissues, a high mechanical strength and good corrosion resistance due to its chemical stability.\textsuperscript{68, 69} However, the inertness of TiO\textsubscript{2} has been questioned,\textsuperscript{30} and recent studies suggest that TiO\textsubscript{2} can activate the immune system which might favor bone formation during healing.\textsuperscript{32}

Moreover, the macro-design and implant shape influence the achievement of high primary stability and for maintaining the stability during the early phases of bone formation. As screw-shaped, threaded implants demonstrated
favorable results, compared to the previous cylindrical or hollow implants,\textsuperscript{6} the commercially available implants today are dominated by this type of macro-design. The threads with tops, valleys and flanks introduce primary stability at insertion in bone similarly for various types of implants, whereas the cutting properties are different between implant systems.\textsuperscript{70-72} Moreover, parallel-walled implants as well as tapered implants are used to fit diverse clinical situations.\textsuperscript{70} In cases with low bone density, the tapered implants may offer higher primary stability compared to straight-walled implants.\textsuperscript{13, 73}

1.3.3.1.1 IMPLANT SURFACE

During the last decades, various surfaces have been commercialized that differ from the original turned, minimally rough surface of the Brånemark system implants. In order to achieve higher survival rates, shorter healing periods and faster treatment modalities the surfaces were modified into rough or moderately rough surfaces, using, for example, blasting, etching, oxidization, or coating procedures.\textsuperscript{10}

The surface characteristics of titanium implants play a critical role for the biological response to the material, including morphology as well as chemical composition. The surface topography can be described in three dimensions in order to depict the microstructures of the surface. Wennerberg and Albrektsson recommend using the height, spatial and hybrid parameters to fully describe the topography and surface enlargement in three dimensions for dental implants. Often, the arithmetic mean deviation of a surface ($S_a$) is used for the height characterization, the developed surface area ratio ($S_{dr}$) for the hybrid description and the density of summits ($S_{ds}$) for the spatial parameter,\textsuperscript{74} in order to distinguish different types of surface enlargements. The original Brånemark implants (Nobel Biocare) with a machined turned surface can be considered minimally rough ($S_a 0.5-1.0\mu m$), whereas the anodically oxidized surface TiUnite$^\text{TM}$ (Nobel Biocare) is considered moderately rough ($S_a 1.0-2.0\mu m$). Rough surfaces are characterized by $S_a >2.0\mu m$.\textsuperscript{75} The surface characteristics further involve physico-chemical properties such as hydrophilicity and nanotopography.\textsuperscript{76, 77}

Histomorphometry has demonstrated bone-to-implant contact (BIC) around implants between 60-90\%\textsuperscript{78} The reported BIC is higher with increased surface roughness as compared to a turned surface, which has been demonstrated in vivo and in human bone.\textsuperscript{78-80} A stronger bone response and faster bone healing has been reported for implants with modified surfaces, in vivo\textsuperscript{75, 81, 82} This has been suggested to be related to increased surface area in contact with bone and
improved cell attachment to the surface, but this is also related to inherent changes of nanotopography as well as the physical and chemical properties from the surface modification process.\textsuperscript{10, 38, 80, 83} This has been further studied in humans with similar results.\textsuperscript{84, 85}

\textbf{1.3.3.2 SURGERY}

The surgical trauma caused during implant insertion needs to be controlled in order to promote bone formation around the implants during the following healing.\textsuperscript{45} Originally, a protocol with meticulous routines was suggested, including the need for proper drilling sequences, the use of a cooling system, and a gentle surgical technique to enable favorable conditions for osseointegration,\textsuperscript{68, 86, 87} protocols that remain essential. The experience of the surgeon may affect the results, as the selection of methods during the surgery also may have an impact indirectly through the bone quality, bone quantity and primary stability.\textsuperscript{5, 88-90} Initial high primary mechanical stability which facilitates bone formation around the implant, can be achieved by using implant-specific drill protocols that depend on the bone quality, and surgical techniques, including under-dimensioned preparation (i.e., the prepared site has a smaller diameter than the implant).\textsuperscript{70, 91} Under-dimensioned preparation can lead to high mechanical stress on the surrounding bone if excessive force needs to be used to insert the implant, leading to compression damages on the bone.\textsuperscript{91, 92} Hence, an insertion force that is too high should be avoided as it can damage tissue, jeopardizing the bone formation around the implant, or resulting in subsequent bone loss. Moreover, post-operative pain after implant insertion has been correlated to increased levels of pro-inflammatory cytokines from peri-implant crevicular fluid (PICF),\textsuperscript{39} findings that were also correlated to failed osseointegration and early implant failure.

\textbf{1.3.3.3 SURGICAL APPROACH – LOADING CONDITIONS}

During the initial healing phase after insertion, implants need a stable bone anchorage that prevents micromovements, which could result in failed bone formation on the implant surface.\textsuperscript{58, 93} The stability of the blood clot in the early stages of bone healing with cell adhesion as well as bone remodeling, might be disrupted if the implant is subjected to undue loading or micromotion.\textsuperscript{94, 95} Therefore, originally all implants were thoroughly submerged underneath the mucosa, and left to heal for several months.\textsuperscript{5} However, if high primary stability can be achieved during implant insertion, implants may be loaded immediately or early after surgery, with acceptable clinical results.\textsuperscript{96-101} In addition, a one-
stage surgical protocol with simultaneous abutment insertion and implant insertion can be used, preferably in the mandible.\textsuperscript{102-105} In the edentulous mandible, immediate, early, and delayed loading yield similar implant survival rates of 94–100\% over 1–5 years.\textsuperscript{99} In the edentulous maxilla, the immediate and early loading protocols are less studied, but reports with implant survival rates of 93–100\% over 1–5 years have been reported.\textsuperscript{99, 100, 106} As a consequence of a two-stage surgery, perforations of the implants through the mucosa can appear in edentulous jaws through decubital ulcers,\textsuperscript{1} and may allow for submucosal bacterial accumulation. Nevertheless, the risk for implant failure is higher for immediately loaded implants, especially in the maxilla and in single implant cases,\textsuperscript{99} and the two-stage, submerged method is still employed.\textsuperscript{107, 108}

1.3.3.4 FOREIGN BODY EQUILIBRIUM

Long-lasting osseointegration has been described in terms of a foreign body equilibrium where the steady state of bone around the implant depends on a balance of the immunological response that, if altered, may lead to bone loss around the implant.\textsuperscript{65} An on-going response to material inserted into living tissue might be at play.\textsuperscript{65, 78} Bone turnover continues throughout life, regulated by bone formation and bone resorptive cells, (e.g., targeted in patients suffering from osteoporosis).\textsuperscript{109} The achieved integration of an implant must be maintained. As the immune system is adapted to continually respond to the intrusion of foreign material such as an implant, the key to a successful implantation is to keep the environment stable so the integration is established and maintained.\textsuperscript{33, 65} Donath et al. conclude that “the numerous clinical, radiographic and morphological studies on implants are specific investigations of the foreign body reaction. To our knowledge, there is no biomaterial which is absolutely inert”.\textsuperscript{30}
1.4 FAILURE OF OSSEOINTEGRATION

1.4.1 EARLY IMPLANT FAILURE

Implant loss that occurs at an early stage after insertion is often referred to as early implant failure. The definition of early differs between studies, but it is recognized as a failure to establish bone formation around the implant.\textsuperscript{47, 110, 111} Early implant failures can be manifested through pain, swelling, mobile implant, infection or radiographic findings of peri-implant radiolucency and/or bone loss. Factors related to early implant failure are closely related to the above discussed factors identified as critical for the formation of bone around implants.

1.4.1.1 FACTORS RELATED TO EARLY IMPLANT FAILURE

1.4.1.1.1 HOST-RELATED FACTORS

Variations in the host response have been demonstrated to be involved in several conditions throughout the body, including periodontitis and peri-implant bone loss.\textsuperscript{112} Patient related variables such as systemic disease and bruxism have been suggested to be associated with higher risk for early implant failure.\textsuperscript{113-115} However, clinical studies report inconclusive results regarding the correlations between osseointegration and systemic diseases. Diabetes mellitus, rheumatoid arthritis, and osteoporosis have been correlated with increased risk of early implant failure (i.e., the failure of bone formation around inserted implants).\textsuperscript{62, 116, 117} However, a recent systematic review failed to demonstrate any correlations between implant failure and several comorbid conditions (e.g., osteoporosis, diabetes mellitus, rheumatoid arthritis, HIV, neurologic disorders, cardiovascular disease and hypothyroidism),\textsuperscript{118} corroborating earlier findings.\textsuperscript{119} These studies indicated that other factors may influence the outcome (e.g., implant surface characteristics) as the results differed between different cohorts of patients divided by type of implant surface.\textsuperscript{116, 119} Moreover, bone metabolism can also be affected by hypothyroidism, although it has not been correlated with higher risk of early implant failure.\textsuperscript{120}
1.4.1.1.2 MEDICAL TREATMENT

Medical treatment with, for example, proton-pump-inhibitors (PPI) has been related to a higher risk for implant failure. These effects might be related to effects on the bone metabolism. Serotonin selective re-uptake inhibitors (SSRI) have been investigated although with conflicting results. At least one study suggests that SSRI was correlated with increased risk for implant failure while others indicate the opposite. Moreover, medical treatment with anti-hypertensive drugs, bisphosphonates and non-steroidal anti-inflammatory drugs have not been statistically correlated to implant failure, however, at least one other study found that osteoporosis treated with bisphosphonates was associated with implant failure. In the above-mentioned studies, the results do not discriminate between early and late implant failures, although most of the studies report failures occurring within 12–14 months after implant insertion. Moreover, implant surgery without use of pre-operative antibiotics has demonstrated increased risk of early implant failure, however, also conflicting results have been reported.

1.4.1.1.3 AGE

Theoretically, older age can lead to systemic disorders that could interfere with bone formation and healing ability around implants, but this has been contradicted by clinical data. Older age at implant surgery is not correlated with higher risk of early implant failure. On the contrary, the older patient group can represent lower incidence of failure as compared to the younger cohort. Middle-aged patient groups have also presented with a higher risk for implant failure than the old and young groups, respectively. However, the age factor alone may be of less interest than other confounding variables, as the situation for a clinical case with a single implant replacing a tooth lost due to trauma is far different from a completely edentulous jaw due to severe periodontitis at a relatively young age.

1.4.1.1.4 SMOKING

Smoking negatively influences the survival of dental implants as well as several other physical conditions including wound healing and decreased bone density. Smoking, and specifically nicotine, is believed to exert a detrimental effect on the vital angiogenesis and osteogenesis during bone healing, critical processes for bone formation around implants. Moreover, smoking has also been coupled to increased risk of tooth loss and periodontitis. There is a detrimental effect on the osseointegration phase of inserted dental implants, as seen on findings from retrieved human samples, and the impact on implant survival is further reflected in several clinical reports.
1.4.1.1.5 IMPLANT SURFACE
Clinical data have demonstrated improved implant survival rates for implants with modified surfaces as compared to the turned surface. Decreased rates of early implant failures have been suggested with implants with moderately rough surfaces compared to rough or minimally rough surfaces. Furthermore, implants with rough surfaces and hydroxyapatite coatings displayed promising results with high bone-to-implant contact in early phases of bone formation, but resulted in poor clinical outcomes with increased rates of peri-implant bone loss and implant failures due to debonding of the coating layer.

1.4.1.1.6 SURGERY
Faulty procedures during implant insertion such as improper handling of the tissues, heat induced damages in the bone during the surgical trauma, and lack of aseptic routines can compromise the healing process, posing a risk for implant failure. Also, biological aspects such as bone quality, bone quantity, and primary stability of the implant at insertion can affect the osseointegration. Bone quality and quantity can be categorized using the system developed by Lekholm and Zarb, which identify different degrees of bone resorption and bone density. High bone density within the trabecular bone and/or a large proportion of cortical bone represent the opposite of low bone density with sparse trabecular pattern and thin cortical layer. Bone quality represented at both ends of the scale have been associated to higher incidence of implant failure (i.e., very low bone density or very high bone density). Early implant failure is more often found in the maxilla, reflecting the softer bone present in the anterior mandible may also induce surgical risks in terms of heat-induced tissue damage because of poor cooling during the drill sequences of site preparation. The degree of primary stability of the implant during insertion can be measured by resonance frequency analysis (RFA), displaying a certain level of implant stability quotient (ISQ), reflecting bone stiffness and implant stability. Low levels of ISQ indicate poor primary stability whereas higher levels indicate high primary stability with subsequent higher chances for osseointegration. Per-operative RFA in conjunction with the insertion torque values obtained during the surgical insertion of implants can be used to assess the status of the inserted implant. Nevertheless, recent implant systems with surface modified implants, altered
implant designs and different drill protocols may introduce better probabilities to achieve high primary stability also in softer bone qualities.\textsuperscript{151, 158}

Moreover, a surgeon’s experience or clinical skills and attitudes may also influence the early failure rates due to the handling of the clinical situation. This is a complex topic that includes consideration of pre-, per-, and post-operative assessments, treatment planning and personal characteristics.\textsuperscript{89, 90, 159}

1.4.1.1.7 MAINTENANCE
The microflora that establishes around the implant soon after insertion need to be minimized in order to prevent infection. Infection after implant surgery, as well as poor healing ability and premature loading could increase the risk for early implant failure.\textsuperscript{93, 128} Wound healing can also be impaired by the presence of plaque and bacteria.\textsuperscript{34} Therefore, a careful program with dental hygiene after implant insertion is recommended. Moreover, it has been recommended to maintain an undisturbed healing for the implants during the initial period after implant insertion. This includes prevention of decubital ulcers and wound dehiscence by careful prosthesis adjustments and pressure relief under prosthesis. Soft relining of the prosthesis can be performed to reassure a pressure-free fit of the prosthesis.

1.4.2 LATE IMPLANT FAILURE
The failure of osseointegration at a later stage, when an implant loses its integration after a period of stable osseointegration, is referred to as late implant failure – i.e., bone around the implant starts to break down.\textsuperscript{65} In many cases, this can be seen as a progressive loss of supporting marginal bone around the implant, which occasionally may lead to total implant failure. The resorption of bone can be crater-like around the implant, most often replacing bone with inflammatory tissue, often bleeding and sometimes including suppuration.\textsuperscript{160} In other cases, the bone loss appears to surround the implant throughout the total length of the implant, visible as a thin space of bone loss around the implant threads observed in a radiograph.\textsuperscript{31}

Failure to maintain osseointegration occurs in a few cases, less frequent than the early failures. Between 0–4% of the implants of different types have been reported to lose bone anchorage.\textsuperscript{11} One systematic review of implant survival in edentulous jaws reported five-year results of 98–99% for maxillary and
mandibular implants, respectively.\textsuperscript{161} Long-term survival can be assumed for turned as well as roughened surface implants,\textsuperscript{3, 55, 57, 162} – e.g., implant survival of 93\% at 25 years and prosthesis survival of 84\% after 25 years.\textsuperscript{3} Analyses from 20 years ago reported that factors such as jaw volume, overload and bone quality are the main explanatory factors for late implant failure.\textsuperscript{163} More recently, host characteristics and progressive marginal bone loss leading to late implant failure as a result of an infectious process have dominated the research; however, a multifactorial etiology is accepted.\textsuperscript{93, 160} Although a causal relationship has been established for biofilm formation and mucosal inflammation,\textsuperscript{164, 165} the definitive conclusion that late implant failure can be attributed only to bacterial infection has not been drawn.

\subsection*{1.4.3 MOLECULAR FINDINGS – CYTOKINES}

Disturbances early in the integration process discussed above can lead to failed bone formation around the implants. If the signaling between cells is disturbed or altered, it may affect integration later in the process.\textsuperscript{4} Molecular findings demonstrate that proinflammatory cytokines IL-6, IL-8, and TNF-\(\alpha\) increase immediately after implant insertion and steadily decrease until day 28.\textsuperscript{39} High levels of proinflammatory cytokines in PICF has been correlated to clinical registrations of patient-reported pain, and early implant failure was associated with lower gene expression of bone remodeling gene CathK and the pro-osteogenic growth factor bone morphogenetic protein BMP-2, in non-smokers.\textsuperscript{39} Furthermore, in a population with generally increased levels of IL-10 during the first 12 weeks after implant insertion, smokers presented with higher levels of IL-1B and lower levels of IL-10 in PICF compared to non-smokers; however, these findings were not correlated to higher risk for early implant failure.\textsuperscript{166} High levels of IL-1B may indicate an upregulated proinflammatory response, which has also been coupled to the presence of plaque accumulation around implants.\textsuperscript{164, 167}

In addition, complications in the process around implants after insertion can be attributed to an imbalance in the RANKL/OPG-ratio. The immune response that is induced by the implantation trauma promotes the introduction of monocytes to the site. After developing into macrophages, they can express RANK, RANKL and M-CSF to induce a self-activated osteoclastogenesis. The activation of osteoclasts can also be induced by IL-1 and TNF-\(\alpha\) without the presence of RANKL, which can lead to a bone degradation process that maintains itself with more available RANKL than there is counteracting OPG, resulting in severe bone loss around the implant.\textsuperscript{40} Clinical studies have found
that, coupled to the chronic inflammation around implants, macrophages are present in bone surrounding the implants, and can be activated in any of the above-mentioned pathways.\textsuperscript{168, 169} Furthermore, a polarization of macrophages has been suggested as a response to the implant: a M1-polarization indicates a pro-inflammatory, acute response to host tissue injury, whereas the M2-polarization is indicates a more reparative activity.\textsuperscript{64} Signals from M1-polarized macrophages have been found at implant sites with peri-implant bone loss, indicating tissue breakdown.\textsuperscript{168, 170}

An altered RANKL/OPG ratio coupled to systemic conditions such as osteoporosis and inflammatory bowel disease has been suggested to affect the bone metabolism and also the response to inserted implants.\textsuperscript{40, 171} In the orthopedic field, osseointegrated titanium implants are used in total hip replacement therapies;\textsuperscript{172} however, these implants differ in many ways from the intraoral cases. For example, orthopedic prostheses are placed within the host tissue without any external communication, whereas the loaded intraoral implant is always in contact with the bacterial environment in the oral cavity through the transmucosal prosthetic reconstruction. Nevertheless, orthopedic implants encounter problems with aseptic loosening of the implant, mostly attributed to peri-implant osteolysis. A recent clinical study found a specific profile of cytokines from patients with aseptic loosening of hip implants, including IL-1β, IL-2, IL-8, IFN-γ, and TNF-α; the anti-inflammatory cytokine IL-10 has also been detected.\textsuperscript{173}

### 1.4.4 PERI-IMPLANTITIS

Clinical signs of inflammation in the peri-implant mucosa, bleeding on probing, suppuration and increased probing depths around implants as a result of bone loss have been described as the diagnosis peri-implantitis. The features of peri-implantitis are often compared with the dental disease periodontitis, which has led to the conclusion that the condition can be related to periodontitis;\textsuperscript{160} however, this conclusion has been debated in the literature lately.\textsuperscript{65, 174} Progressive bone loss can eventually lead to loss of the implant, directly by implant loosening or indirectly by active removal of the implant due to extensive bone loss and poor clinical function.\textsuperscript{31}

Peri-implant mucositis has been defined as inflammation in the peri-implant mucosa diagnosed by findings of bleeding on probing from the peri-implant mucosa, without bone resorption, but sometimes suppuration, erythema, and swelling are present.\textsuperscript{160} Biofilm accumulation can induce mucositis in the
tissues, and clinical resolution of the inflammation can be seen after removal of plaque.\textsuperscript{164, 165, 175} Mucositis is often described as the precursor for peri-implantitis, indicating that poor plaque control may lead to peri-implantitis. However, no evidence has been found for the actual transition from mucositis to peri-implantitis.\textsuperscript{160}

Peri-implantitis has been described as a plaque-associated pathological condition in tissues around dental implants, characterized by inflammation in the peri-implant mucosa along with progressive loss of supporting bone.\textsuperscript{176} However, this definition differs largely among studies due to difficulties reaching consensus as to how to define and grade the inflammation. The condition does not follow the same pattern of progression as periodontitis,\textsuperscript{177} probably because it lacks the evolutionarily developed tissues around teeth, which are broken down during progressive periodontitis.

Histological evaluations of peri-implantitis lesions have demonstrated infiltrate with neutrophil granulocytes, lymphocytes and plasma cells, as well as polymorph nuclear granulocytes and macrophages.\textsuperscript{176} A microbiological cause is assumed; however, the picture of the microbial flora from submucosal samples is still regarded as incomplete.\textsuperscript{176} Various cytokines and biological markers have been detected in samples from PICF and correlated with clinical findings of peri-implantitis lesions. The proinflammatory markers IL-1β and TNF-α have been detected in sites with peri-implant inflammation, but the distinction between mucositis and peri-implantitis has been difficult to draw.\textsuperscript{176} Moreover, other biomarkers (e.g., RANKL, IL-10, and IL-4) have been investigated to distinguish between healthy mucosa, mucositis and periimplantitis, although the findings are inconclusive.\textsuperscript{178} Furthermore, a multi-marker model has been proposed to discriminate between “healthy” and “diseased” implants, where IL-17, IL-10, GM-CSF, TNF-α, and IL-15 among others were included.\textsuperscript{179} Among the studies analyzing cytokines and biologic markers in peri-implant lesions, investigations of PICF samples are used as a standard method, and analyses of bone samples are rare.

Compromised general health, smoking, metabolic syndrome, diabetes and occlusal overload have been correlated with clinical diagnosis of peri-implantitis; however, the results were inconclusive.\textsuperscript{176, 180} Proton pump inhibitors (PPIs) have recently been correlated with higher risk for progressive marginal bone loss.\textsuperscript{181} Periodontitis susceptible patients are often referred to as risk patients for implant rehabilitation, due to the suggested correlation in disease progression in periodontitis and peri-implantitis.\textsuperscript{182} There is strong evidence for a correlation, but there are studies reporting conflicting results.\textsuperscript{176}
The roughened implant surfaces have been suggested to be more prone to peri-implant bone loss, possibly due to the micro-retention of plaque and bacteria. However, factors such as smoking and history of periodontal disease can be related to the differences in bone loss, rather than differences in surface topography, which are of little significance clinically. A Cochrane review found that the prevalence of peri-implantitis at a three-years follow-up was slightly lower for implants with a turned surface. Clinical five-year data from a randomized, controlled clinical trial (RCT) on periodontal susceptible patients, demonstrated good results with only 0.4 mm bone loss after five years, both for implants with turned as well as roughened surfaces. In another meta-analysis, three implant systems with different moderately rough surfaces were compared. Small, but statistically significant, mean bone level changes were found between the groups after one and five years in clinical service.

1.4.5 CONSEQUENCES OF IMPLANT FAILURE

Implant failure can have different consequences depending on the clinical situation and state of edentulousness. A lost implant in a single tooth rehabilitation requires revision surgery to restore the gap, or a different therapy. Meanwhile, if one implant is lost in an edentulous jaw, it is often possible to proceed with the original prosthesis with minor adjustments. However, if several of the supporting implants are removed, the need for revision surgery or another rehabilitating option is inevitable. A report on a 20-year follow-up study found 86% prosthesis survival in edentulous jaws and 92% had prosthesis survival without implant failure. In the 1990s, a survival rate of 92–100% for full-arch bridges supported by turned implants were reported, after 5–15 years of follow-up, and 96% after five years. Moreover, five-year prosthesis survival in edentulous maxillae has later been reported for 97–100% of the study population and 15-year data on edentulous jaws reached 89–100% survival. Technical and biological complications occur, especially in the edentulous jaws as they bear all the load on the implant-supported reconstruction. The complications are usually minor such as chip-off of veneering material or bridge-screw loosening, and can be adjusted chair-side or with assistance from the dental laboratory.

A recent study of a large patient cohort in Sweden, demonstrated that patient satisfaction is generally high after nine years, and that most patients with different types of complications would choose the therapy again despite the complications. These findings agree with other findings.
1.5 RATIONALE FOR THESIS

Although rare, dental implant failures occur. The failure of implants may have a large impact on the individual and the different reasons for dental implant failure are still not fully understood. Several factors involving the titanium implants and surgical techniques as well as the host have been reported, but more knowledge is needed to predict dental implant failure and improve treatment planning. Further understanding of the associated factors may introduce possibilities for preventive measures, which would reduce patient suffering and economical effects in a larger perspective. Moreover, studying the molecular footprint of implants with severe bone loss could help develop predictors for ongoing bone loss around dental implants.

This thesis hypothesizes that patients who experience early implant failure differ in the anamnestic and treatment-related data compared to patients who have no implant failure. We also hypothesize that there would be differences in gene expression between implant sites with severe bone loss and unaffected bone.
2 AIM

This thesis aims to improve the understanding about factors related to dental implant failure. This thesis mainly focuses on early implant failure, that is depending on the failure to establish osseointegration, but it also looks at late implant failure where implants lose their surrounding bone after some time in function.

Specifically, this thesis has the following aims:

- To present an overview of the incidence of implant failure in a large clinical patient material, describing the incidence of first implant failure in relation to the entire group of rehabilitated patients over a period of 28 years of follow-up. (Study I)

- To investigate the incidence of early implant failure in edentulous jaws and to identify possible risk factors associated with early implant failure in the entire group of patients with edentulous jaws rehabilitated with dental implants. (Study II)

- To further investigate potential risk factors for early implant failure in a group of patients with edentulous jaws with early implant failure matched to a patient group with no implant failure, by analyzing several patient- and implant-related factors. (Study III)

- To analyze the gene expression of selected biomarkers in bone and PICF surrounding implants exhibiting severe bone loss, and to compare this with the expression in unaffected bone samples within the same patients. (Study IV)
3 PATIENTS AND METHODS

The present thesis was based on patient data collected at a specialist referral clinic: the Brånemark Clinic, Public Dental Service, Region of Västra Götaland, Gothenburg, Sweden. The Studies I, II and III were retrospective registry studies based on patient files from the clinic. Study IV was a prospective experimental study and data were collected from patients subject to implant removal at the Brånemark Clinic.

3.1 DEFINITION OF IMPLANT FAILURE

An implant that was removed for any reason was categorized as a failed implant. The reasons for removal were: pain, mobile implant, radiographic signs of peri implant bone loss, fracture, and extensive marginal bone loss. The reported failures included both spontaneous exfoliations of implants and clinical/surgical removals by clinical professionals.

Early implant failure was defined as an implant that was removed at any time after implant insertion surgery up to first annual control visit at one year after connection of the prosthetic reconstruction (i.e., within the first year of function).

Late implant failure was defined as an implant removed after more than one year of prosthetic functioning – i.e., after the one-year control visit.

3.2 PATIENTS

3.2.1 PATIENT GROUPS IN STUDIES I, II, III

3.2.1.1 DATA COMPILATION, STUDIES I, II, III

Data were compiled from patient files in the analogue and digital registries at the Brånemark Clinic. First, all patients with implant failure of any kind were identified by searching the registries. Each failure was categorized into one of the following groups: completely edentulous, partially edentulous, or single implant.

Patient files from the early rehabilitations many years ago were not physically
at the clinic when data compilation started. Therefore, the regional archive in the city of Vänersborg, Sweden, was visited twice to collect patient data files. These files were all returned in original state to the archive after collection of information.

The time point of each implant failure was determined after going through the patient files. The time point of the first implant failure for each patient and subsequent implant failures were recorded. However, the time point for the first implant failure determined the categorization of the patients as each patient was counted once per jaw, also in cases where multiple implants had been inserted at the same time. The calculations were based on the patient or jaw as a unit, not the implant.

For the implant surgical interventions, information regarding number of implants, type of surface (turned and moderately rough), length of the implants, and operating surgeon were recorded. For patients in Study II and Study III, date of implant surgery, abutment connection/second stage surgery, first implant failure, prosthesis insertion, baseline radiographic examination and first annual follow-up-visit were recorded. In Study III, information from the pre-surgical examinations were recorded regarding patients’ general health status, presence of allergies, intake of medication, smoking habits, signs or diagnoses of bruxism, reasons for tooth loss (caries, periodontitis, trauma, agenesis, etc.), time edentulous, and condition of the opposing jaw.

3.2.1.2 MATCHING PROCEDURE, STUDY III
The results from Study II were further developed in Study III. The findings of statistical significance were the basis for matching of patients in Study III. All patients who were rehabilitated in an edentulous jaw were gathered into a data file for matching procedure, including in total 4090 patients (4784 surgical interventions in 2663 mandibles and 2121 maxillae). The total number of included failures were 408, leaving a total number of 4376 rehabilitated jaws for the matching procedure. The matching procedure was performed by computer following the principle of closest match according to gender, age, type of jaw, type of implant surface, and year of surgery. Gender, jaw, and surface were always an exact match, whereas age and year of surgery differed maximally +/–3 years with only four exceptions. Thus, 408 matched control patients were included in the study and compared to the case patient group. After compilation of the total study group, information on the selected variables were collected.
3.2.2 PATIENT GROUP IN STUDY IV

3.2.2.1 INCLUSION

Ten patients scheduled for surgical implant removal at the Brånemark Clinic were recruited to the study. The implant insertion was either performed at the Brånemark Clinic or the patient had implant insertion previously performed at another clinic, and was referred to the Brånemark clinic due to peri-implant bone loss. One implant per patient was included. The implants had been diagnosed with ongoing severe bone loss and poor prognosis. (Figures 1 and 2)

![Image](example.png)

*Figure 1. Example of clinical manifestation of inflammation, suppuration and bone loss around dental implants in the front region of maxilla. Photograph courtesy of Dr. Alberto Turri.*

![Image](example.png)

*Figure 2. Example of radiographic examinations before sampling and implant removal.*

Participation was voluntary, and all patients signed an informed consent form. Partaking in the study did not affect the patients’ treatment.

One patient was excluded due to incomplete sampling, so the patient group consisted of nine patients. The patient group is described further in Study IV.
3.3  SAMPLING AND ANALYSIS METHOD  
STUDY IV

Study IV, a pilot study, was performed to study the technique and sampling methods for bone and peri-implant crevicular fluid (PICF) as well as to investigate preliminary results of gene expression in bone surrounding dental implants with severe bone loss, compared to the expression from unaffected bone in the same patients.

3.3.1  SAMPLING PROCEDURE

At the appointment for implant removal, PICF samples (collected with sterile paper points) and two bone samples were collected from each patient. The first bone sample was harvested from bone bed at a distance from the implant site in order to collect bone with normal appearance, and this unaffected bone was used as a control sample (CB). Bone tissue adjacent to the implant was harvested to represent bone from an implant with severe bone loss (i.e., test sample) (BL). The samples were immersed into a transport medium (RNALater preservation medium, Qiagen, Hilden, Germany) and shipped to the analyzing laboratory. This process is described further in Study IV.

3.3.2  QPCR ANALYSIS

The gene expression analysis was performed using a quantitative real-time Polymerase Chain Reaction (qPCR). qPCR can detect expressed biological markers (e.g., the cytokines present in body fluid or tissue) even when expressed in small quantities. The technique for the present analysis is described in Study IV.

3.3.2.1  qPCR TECHNIQUE

The test method was developed in collaboration with and performed by an external test laboratory, TATAA Biocenter, Gothenburg, Sweden. First, RNA was extracted from samples using Qiagen RNeasy Micro Kit No. 74004 (Qiagen GmbH, Solna, Sweden) according to the manufacturer’s instructions. Samples were stored in –80 °C before further analyses.

Reverse transcription of RNA was performed according to manufacturer’s instructions with TATAA Grandscript cDNA synthesis kit (#A103, TATAA Biocenter AB, Gothenburg, Sweden). The qPCR and standard curve analyses were performed in 10-μl reaction volumes on a CFX384 (Bio-Rad Laboratories Inc., Hercules, USA) with TATAA SYBR GrandMaster Mix (TATAA
Biocenter AB, Gothenburg, Sweden). Pipetting was performed by robot (EpMotion 5070, Eppendorf, Germany). The ValidPrime™ concept was used to monitor and correct contamination of gDNA in the analysis.197

3.3.2.2 SELECTION OF MARKERS
Cytokines and biomarkers were selected to illustrate the ongoing molecular and cellular activity around the implants and the state of the surrounding tissue, in bone and PICF. Proinflammatory markers (e.g., IL-1β, IL-8, IL-10, IL-17, TNF-α, sTREM1 and PGLYRP), and two anti-inflammatory markers IL-4 and IL-13 were analyzed. Bone metabolism markers (e.g., OPG, RANKL, OC, TRAP and Cath K) and tissue degradation markers (NE and MMPs) were also included. In addition, several reference genes were selected to verify the relative gene expression in the qPCR-analysis, this selection was performed in the Reference Gene selection tool in the BioRad Maestro 2.0 software (BioRad Laboratories Inc., USA).

3.3.3 INTERPRETATION OF QPCR-ANALYSIS
The cycle threshold of quantification (Cq) demarcates the magnitude of the expression of genes.198 Relative gene expression was calculated by the ΔΔCq-method, which validates the quantification of genes between biological groups (e.g., from different tissues) compared to the reference genes.199 Up-regulation ≥ 2-fold was considered to be clinically relevant.199

3.4 STATISTICS
3.4.1 STUDY I
Data were presented with descriptive statistics. Analyses of differences between groups were performed with Chi² test and Student's t-test. Statistical significance was considered at P<0.05. All calculations were performed at patient level or jaw level with the event per patient or included surgical intervention as basis for analysis (i.e., not the implant).

3.4.2 STUDY II AND STUDY III
Analyses of data in Study II and Study III were performed with multivariable logistic regression analyses. A binary outcome, such as early implant failure (Yes/No) gave the opportunity to use the logistic regression model as it allowed for the correlation of the independent variables with the dependent variable implant failure. The results are presented as Odds Ratios (OR) with a 95% Confidence Interval (CI). The OR express probability for early implant failure for one group compared to the other group with respect to the included variables, when variables are dichotomous. For non-dichotomous variables, OR expresses probability for one (1) unit difference. OR with a CI not including 1 (one) was considered statistically significant.
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3.4.2.1 VARIABLE SELECTION STUDY II
In Study II, 4615 included jaws were analyzed. All analyses were performed using the jaw as the statistical unit. That is, all edentulous jaws were analyzed that had been rehabilitated with dental implants at the clinic and that complied with the inclusion criteria. No analyses were performed on the implant level.

Information on all 4615 jaws/patients was available for several variables: date for surgical insertion of implants, patient’s age at implant insertion, patient gender, type of jaw (maxilla/mandible), type of implant surface (turned implant surface/moderately rough implant surfaces), and number of inserted implants per jaw. These variables were included in the multivariable logistic regression model in a stepwise manner. First, the three dichotomous variables (gender, type of jaw, and type of surface) were included. Second, the variables age and number of implants were included one at a time. After inclusion of the variables, a control for interaction between variables demonstrated a interaction effect between the variables type of jaw and type of surface, and
this interaction was included in the final model. The contribution of each variable to the final model was tested with a Wald Chi² test. A goodness-of-fit test according to Hosmer-Lemeshow was performed, which supported the employment of the final model.²⁰⁰

### 3.4.2.2 VARIABLE SELECTION STUDY III

In Study III, information regarding the included patients (408 case patients and 408 control patients) were available for many anamnestic or clinical variables. Variables with more than 50 observations were included in the univariate tests for statistical reasons, with a few exceptions. Five variables (Table 1) were included based on clinical relevance, and the number of observations were 36–48. Each variable was tested with Fisher’s permutation test (cases versus controls) for further selection of variables into the multivariable logistic regression. Variables with $P < 0.05$ were included in the multivariable logistic regression model with forward selection without having all variables in the model at the same time to avoid overfitting of the model and false significant results.²⁰¹

*Table 1.* Variables with <50 observations, included in the univariate testing for further variable selection.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnoses (n)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup Asthma / COPD</td>
<td>28</td>
<td>17</td>
</tr>
<tr>
<td>Subgroup Hypo-/Hyperthyreosis</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>Subgroup Rheumatic disease</td>
<td>34</td>
<td>14</td>
</tr>
<tr>
<td><strong>Medications (n)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broncho dilating drugs</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>Levothyroxine, thyroid medication</td>
<td>27</td>
<td>12</td>
</tr>
</tbody>
</table>

### 3.4.3 STUDY IV

The results from the samples from the nine patients were gathered and analyzed according to Control Bone sample (CB), Bone Loss sample (BL), and Peri-Implant Crevicular Fluid sample (PICF). Log-values of the $\Delta \Delta C_q$ were analyzed using the built-in t-test in the analysis software of the BioRad CFX Malin Olsson Malm²⁷

²⁰⁰ Maestro 2.0. Upregulation or downregulation ≥2-fold was considered clinically relevant and statistical significance was set at $P < 0.05$.²⁰⁹

²⁰¹ For the study IV, the MIQE guidelines for reporting of qPCR-studies were followed.²⁰⁸

Funding was granted from Nobel Biocare, Public Dental Service Region Västra Götaland, Wilhelm and Martina Lundgren Foundation, Handlanden Hjalmar Svensson Foundation, Sylvan Foundation, Felix Neubergh Foundation and Gothenburg Dental Society.
On dental implant failure and patient-related factors

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3.5 ETHICAL APPROVAL

Ethical approval was granted for the studies by the Regional Ethical Review Board, Dnr 197-12 (Studies I, II and III) and Dnr 154-12 (Study IV). For the retrospective studies (Studies I, II and III) the STROBE guidelines for clinical studies were followed. For the study IV, the MIQE guidelines for reporting of qPCR-studies were followed.

Funding was granted from Nobel Biocare, Public Dental Service Region Västra Götaland, Wilhelm and Martina Lundgren Foundation, Handlanden Hjalmar Svensson Foundation, Sylvan Foundation, Felix Neubergh Foundation and Gothenburg Dental Society.
4 RESULTS

The four studies were based on various patient cohorts at the Brånemark Clinic and can be seen as a funnel with a gradual approach (Figure 3). First, the total patient group was included to investigate the overall incidence of implant failure (Study I). Thereafter, all edentulous jaws rehabilitated with implants were included and analyzed for some primary variables related to the probability for early implant failure (Study II). Subsequently, all edentulous jaws with early implant failure were matched to a group with no implant failures (neither early nor late) and analyzed regarding to numerous patient- and treatment-related variables (Study III). Finally, a group of patients with implants planned for removal due to severe bone loss were included in a pilot study that investigated the gene expression in unaffected bone, bone from implant site with severe bone loss, and peri-implant crevicular fluid, PICF (Study IV).

4.1 PATIENT GROUPS

Figure 3. Overview of the included studies in the thesis.
4.2 STUDY I

For 27 years (1986–2012), 10,719 surgical interventions with implant insertion (8528 individual patients, and 39,077 implants) were performed at the Brånemark Clinic. Of the rehabilitated jaws, 9% were registered with implant failure. Of these, 69.4% of the jaws had their first implant failure from implant insertion through the first year after prosthesis insertion. After the first failure, 26.8% of the treated jaws had a second event of implant failure, and 8.6% had a third intervention for implant removal. In total, 1641 (4.3%) of all the inserted implants at the clinic failed. There was a large variation of the annual implant failure rate within the total patient group despite seemingly similar clinical conditions (Figure 4). A higher number of implant failures was registered in the maxilla compared to the mandible ($P<0.05$) (Figure 4). The introduction of implants with a moderately rough surface was correlated to a reduced incidence of early implant failure, compared to implants with a turned surface, in the maxilla as well as in the mandible ($P<0.05$).

![Figure 4](image_url)

*Figure 4. Distribution of implant surgeries that resulted in early implant failure: from implant insertion up to first annual control-visit; (i.e., one year after prosthesis insertion). All rehabilitated jaws with early implant failure are reported in percent of total number of performed surgeries during each year. (Reprint with permission from Clinical Implant Dentistry and Related Research)*

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4.3 STUDY II

For 28 years (1986-2013), 4615 edentulous jaws in 3974 patients were rehabilitated using a total of 25,031 implants. Early implant failure was registered in 8.6% of these jaws (Figure 5).

![Flow chart](image)

*Figure 5. Flow chart describing patient groups in Study II, including patients from the total population of rehabilitated patients at the clinic and selecting edentulous patients with early implant failures. N = numbers of jaws/numbers of implants. (Reprint with permission from Journal of Prosthodontics.)*

Five variables were associated with increased probability for early implant failure (Table 2). The variable implants with a turned surface was associated with a higher probability for early implant failure as well as the variable type of jaw: maxilla. Furthermore, the variable younger age at implant insertion was associated with higher probability of early implant failure compared to an older age for patients rehabilitated with implants with moderately rough surfaces.

Lower probability of early implant failure was found for implants with a moderately rough surface, and there was an interaction effect between the type of jaw and the type of implant surface where implants with a turned surface in the maxilla displayed the highest probability for early implant failure. The
probability of early implant failure did not differ between implants with different surfaces (turned or moderately rough) when inserted in the mandible.

Table 2. Results from the multivariable regression analysis, presented with Odds Ratio (OR) with 95% Confidence Interval (CI). P<0.05 statistically significant. *(Reprint with permission from Journal of Prosthodontics)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio, OR</th>
<th>95% CI</th>
<th>P-value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.955</td>
<td>0.77; 1.18</td>
<td></td>
<td>Non-significant</td>
</tr>
<tr>
<td>Jaw type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandible, moderately rough</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandible, turned</td>
<td>1.49</td>
<td>0.77; 2.89</td>
<td></td>
<td>Non-significant difference for the surfaces in the mandible</td>
</tr>
<tr>
<td>Maxilla, moderately rough</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maxilla, turned</td>
<td>3.51</td>
<td>2.27; 5.42</td>
<td>*</td>
<td>Significantly higher odds for turned implants in the maxilla</td>
</tr>
<tr>
<td>Type of surface</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turned, mandible</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turned, maxilla</td>
<td>5.93</td>
<td>4.21; 8.36</td>
<td>*</td>
<td>Significantly higher odds in maxilla with turned implants</td>
</tr>
<tr>
<td>Moderately rough, mandible</td>
<td>2.52</td>
<td>1.19; 5.34</td>
<td>*</td>
<td>Significantly higher odds in maxilla with moderately rough implants</td>
</tr>
<tr>
<td>Moderately rough, maxilla</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, increase by 10</td>
<td>0.9</td>
<td>0.82; 0.99</td>
<td>0.028 *</td>
<td>10% lower odds for every 10 years of increased age.</td>
</tr>
<tr>
<td>Number of implants</td>
<td></td>
<td>0.0045 *</td>
<td></td>
<td>Significant impact on the odds for early implant failure</td>
</tr>
<tr>
<td>Interaction effect (surface/jaw)</td>
<td></td>
<td>0.034 *</td>
<td></td>
<td>Significant interaction on the odds for early implant failure</td>
</tr>
</tbody>
</table>

Most of the early implant failures occurred before prosthesis insertion for implants with a turned as well as a moderately rough surface, and a smaller number of implant failures were recorded after prosthesis insertion up to the one-year control visit. Prosthetic rehabilitation could be completed as planned despite implant removal in the majority of the jaws with early implant failure without complementary implant surgery.
4.4 STUDY III

In total, 408 case patients and 408 control patients were included in the study. All included patients had edentulous jaws that had been rehabilitated with dental implants at the clinic between 1986 and 2016. The patients in the case group had been identified with at least one event of early implant failure (i.e., implant failure occurring after implant insertion up to the first annual control-visit one year after prosthesis insertion). According to inclusion criteria, the control patients were matched to the cases from the remaining patient group with edentulous jaws with dental implants (Table 3).

Table 3. Distribution of included patients, cases, and matched controls.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turned implant surface, maxilla</td>
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<td>76</td>
</tr>
<tr>
<td>Moderately rough surfaces, maxilla</td>
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<td>40</td>
</tr>
<tr>
<td>Moderately rough surfaces, mandible</td>
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</tbody>
</table>

In total, 58 variables were included for univariate testing. Of these, 20 variables were statistically significant ($P<0.05$) and therefore were included in the subsequent multivariable logistic regression analysis.

4.4.1 MULTIVARIABLE LOGISTIC REGRESSION

In the case-control analysis, nine variables were found to be associated with higher probability for early implant failure ($P<0.05$). Variables with anamnestic background such as smoking, systemic disease, allergy (total group), food allergy, and intake of analgesic drugs were associated with higher probability for early implant failure. Moreover, four treatment-related clinical variables were associated with early implant failure: low primary stability, reduced bone volume, healing complications, and implants in the opposing jaw. Table 4 lists the Odds Ratios for the statistically significant results from the multivariable logistic regression analysis, including the results from a sensitivity analysis when controlling for the matching variables age, type of jaw, and type of implant surface.
On dental implant failure and patient-related factors

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### Table 4.

Results from the multivariable logistic regression analysis, including the results when controlling for the matching variables age, type of jaw, and type of implant surface. In the analysis, 20 variables were included; of these, nine were statistically significant. For further details, refer to Study III.

#### MULTIVARIABLE LOGISTIC REGRESSION ANALYSIS

<table>
<thead>
<tr>
<th></th>
<th>MAIN ANALYSIS</th>
<th>SENSITIVITY ANALYSIS (controlled for matching factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td><strong>ANAMNESTIC VARIABLES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic disease</td>
<td>1.81 (1.26, 2.59)</td>
<td>1.78 (1.22, 2.59)</td>
</tr>
<tr>
<td>Medicine: analgetics other than NSAID, e.g., paracetamol</td>
<td>2.37 (1.11, 5.07)</td>
<td>2.49 (1.16, 5.35)</td>
</tr>
<tr>
<td>Allergies</td>
<td>1.93 (1.16, 3.21)</td>
<td>2.29 (1.34, 3.90)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>5.59 (1.10, 28.42)</td>
<td>5.53 (1.07, 28.47)</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.32 (1.62, 3.32)</td>
<td>2.32 (1.59, 3.39)</td>
</tr>
<tr>
<td><strong>CLINICAL CONDITIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status of the opposing jaw: edentulous jaw with implants</td>
<td>1.69 (1.05, 2.72)</td>
<td>1.70 (1.05, 2.75)</td>
</tr>
<tr>
<td>Primary stability of inserted implants</td>
<td>2.31 (1.43, 3.75)</td>
<td>2.51 (1.51, 4.16)</td>
</tr>
<tr>
<td>Bone volume: little vs severe resorption</td>
<td>10.93 (4.11, 29.02)</td>
<td>9.07 (3.57, 23.01)</td>
</tr>
<tr>
<td>Healing complications</td>
<td>14.41 (8.12, 25.56)</td>
<td>14.51 (8.08, 26.04)</td>
</tr>
</tbody>
</table>
4.5 STUDY IV

In the analysis of bone samples from sites with severe bone loss versus sites with unaffected bone, there was an upregulation of various biological markers in samples from bone loss sites compared to unaffected bone samples (e.g., pro-inflammatory cytokines, and chemokines) as well as bone degradation markers. A downregulation was observed for the osteoprotective marker. In the analysis of PICF samples versus bone samples from unaffected bone, the PICF samples demonstrated upregulation of pro-inflammatory markers compared to unaffected bone. However, relative to the analysis of bone loss samples, the findings from the PICF analysis did not correspond fully, even though they were collected from the same sites with severe bone loss. For detailed information, refer to Study IV. Figure 6 illustrates a retrieved implant, still attached to the fixed partial denture.

Figure 6. Retrieved dental implant due to severe bone loss, along with the partial denture. Photograph courtesy of Dr Alberto Turri.
5 DISCUSSION

5.1 METHODOLOGICAL DISCUSSION

5.1.1 STUDY GROUPS (STUDY I, II, III)

5.1.1.1 INCLUSION OF PATIENTS, STUDY I, II, III

All rehabilitated patients at the Brånemark Clinic were invited to participate in the clinic’s follow-up program. This program included a first regular follow-up-visit one year after the prosthesis insertion with a clinical and radiographic examination. Most of the patients attended these visits. The time that passed from implant surgery to prosthesis insertion differed due to variations in the treatment protocols for healing and loading for the different rehabilitations and because of changes in treatment regimens over time. Hence, the actual follow-up times from implant surgery to first control visit or first implant failure for the patients were expected to be different, which could give variations in the incidence of early and late implant failures, respectively, in the inclusion for the studies in the present thesis. One rationale for dividing the patients in an early and late failure group was among other reasons related to the wish to create patient groups of manageable sizes. Moreover, it was speculated that there might be variations in the factors involved in early failures as compared to late implant failures, where the long-term effects are studied.

Some studies report early implant failure up to the time of abutment connection; however, this thesis extended the observation period past this time point to include all patients who were thought to have had a problematic osseointegration process. The cut-off at the one-year follow-up was made because it offered a systematic way to collect anamnestic, radiographic and clinical examination data. In addition, all failure cases occurring within this time range would be included, also those rehabilitated with one-stage-protocols with abutment connection at the time of implant insertion. The actual follow-up time from implant insertion to one-year visit ranged from implant insertion to 1.67 years after insertion, for example, in cases where the first annual control visit was delayed or when the treatment time was prolonged. To identify all cases where the osseointegration process had failed, the follow-up time needed to go further than up to prosthesis insertion or abutment connection. We presupposed that the events that occurred during the first year of bone remodeling and healing after implant insertion were related to the establishment of the osseointegration as opposed to the events that occurred during later phases where the implant had been surrounded by a bone integration but eventually displayed bone loss. Consequently, the exact
follow-up time in the present study is not one year from prosthesis insertion for all patients. However, the retrospective nature of Studies I, II, and III limited the possibilities to establish exactly the same follow-up time for all patients.

In addition to the first annual control visit, all patients were invited to participate in an individualized follow-up program. All patients were invited to a follow-up visit five, ten, and fifteen years from prosthesis insertion, and further on every five years. Individual needs sometimes required more than the standard protocol, so some patients were seen more often. For practical reasons, the scheduled appointments were occasionally not on exact annual intervals.

5.1.1.2 INCLUSION FOR IMPLANT REHABILITATION AT THE BRÅNEMARK CLINIC

Relative contraindications for implant treatment have been considered, including psychological reasons, irradiation therapy towards head and neck, and severe systemic disease. However, implant rehabilitation at the Brånemark Clinic was possible for most patients throughout the years, and few patients were denied implant treatment. Few exclusion criteria give external validity to our studies, and the results thus may provide a solid base for measuring the effectiveness of implant treatment in totally edentulous jaws when applying the same criteria. However, the population distribution could be skewed as a result of the fact that only edentulous jaws or patients were included, or because the clinic is a specialist clinic that requires referrals. Moreover, the patients referred to the clinic may represent a population that present more challenging clinical conditions. Speculatively, the large spread of surgical and prosthodontic caregivers, the broad inclusion of patients, and the large time span strengthens the possibilities for external validity.

5.1.1.3 MATCHING PROCEDURE, STUDY III

Patients in the study group were included if they had experienced an implant failure up to the one-year control visit. To match this cohort, the matched control patients needed to have follow-up data until one-year control visit or longer to conclude that no implant loss had occurred. Control patients who had shorter follow-up time were excluded. Of the 408 control patients that were selected in the matching procedure described in Study III, 79 needed to be replaced after the first matching procedure, to satisfy the inclusion and exclusion criteria. This replacement was performed complementary from the
database of all rehabilitated edentulous jaws by following the matching variables age, gender, year of surgery, type of jaw, and type of implant surface. Replacement was needed for the following reasons: lost to follow-up due to any reason, registrations of late implant failure, major bone grafting procedures, and missing or incorrectly registered data.

5.1.1.4 VARIABLE SELECTION STUDY III
For selection of variables into the multivariable logistic regression, different approaches can be adopted, and the choice of approach is often considered a critical part of the data analyses. For example, selection could be made by strictly using the P-values from the univariate tests or using the clinical relevance for the respective variables. Most researchers recommend including as few variables as possible in the final model to minimize the risk of overfitting the model and false significances.²⁰¹

Moreover, the right variables need to be included, and to ensure this a generous inclusion of variables from the first univariate step, might be applied in order not to exclude possibly significant variables. One possibility could be to include variables with \( P<0.2 \) from the univariate analyses. If this approach is used, correction for multiple testing could be used when testing many variables (e.g., the Bonferroni correction). This approach would lead to a higher \( P \)-value for the respective variables, excluding the least contributing variables. In the present analysis, we selected all variables with \( P<0.05 \) from the univariate analyses without the Bonferroni Correction, to ensure a more generous inclusion of variables in the final model. Furthermore, a forward selection of the variables into the final model was adopted to avoid having too many variables in the model simultaneously. As in all studies, models merely represent a theory about a problem, and cannot claim to be the truth, but rather an estimate in the study population.

In the present study, the prevalence of bruxism, history of periodontitis and the distribution of occlusal forces have not been evaluated, due to the nature of the retrospective approach. Information on these variables were inconsistently reported in the patient files and hence, bias would be introduced if included for analysis.
5.1.2 LEVEL OF ANALYSIS – STUDIES I, II, III
In the present studies, the results were presented on the patient level or the jaw level in contrast to much published data that have reported results on the implant level. Reporting on implant level may introduce a problem in the evaluation of data as implants cannot be considered independent when placing several implants in the same patient or jaw. Different methods can be adopted to adjust for this (e.g., a generalized estimating equation (GEE) or randomizing one of the implants in a patient). However, using the patient as the unit omits the need for such statistical corrections, as the effect of clustering of complications within patients is decreased.

5.1.3 STUDY DESIGN, STUDY IV
Study IV was designed and performed as a pilot study, to refine the clinical methodology with bone biopsies and PICF sampling as well as the methods for analysis. The sampling procedures with PICF have been widely used in dentistry, whereas the collection and analysis of peri-implant bone biopsies have not been described earlier. The findings from Study IV must be interpreted with caution because of the small sample size and the characteristics of a pilot study.

5.1.4 ETHICAL CONSIDERATIONS
All patient files were carefully searched and handled with the patients’ integrity and confidentiality in mind. No information regarding specific patients can be coupled to any individual person (Studies I, II, and III). Sampling procedures (Study IV) were carefully performed in order to preserve any tissues that could be used for future rehabilitations.
5.2 GENERAL DISCUSSION

5.2.1 FACTORS RELATED TO EARLY IMPLANT FAILURE – STUDIES I, II, III

During the proceeding of the studies included in the present thesis, several factors related to implant failure were found. First, 69% of all first implant failures occur early – i.e., within one year after the prosthesis insertion (Study I). This has been covered in the literature previously although sometimes with contradictory results, possibly due to different cut-off-points for early or late failure.\textsuperscript{136, 213} This thesis interprets failure as the inability to establish osseointegration after implant insertion. The results further showed differences in the number of implant failures per year during a 27-year inclusion period, even though the methods and number of patients were similar. Hence, the importance of including longer time periods to improve the reliability of findings has been demonstrated (Study I).

Moreover, the incidence of early implant failure was higher in the maxilla compared to the mandible, especially when using implants with a turned implant surface (Study I). For the edentulous jaws, the probability for early implant failure was associated with type of jaw, type of implant surface, and age at implant insertion (Study II). Hence, factors related to early implant failure were correlated both to the implant and the patient (Studies I and II), findings that correlate with other studies.\textsuperscript{110} Furthermore, there was also an interaction between the variables type of jaw and type of surface, suggesting that implant rehabilitation in the maxilla especially benefit from the modified implant surface with moderately rough characteristics (Study II). The implant surface and type of jaw have been discussed previously and have been confirmed by the present study.\textsuperscript{11, 161, 214} Age, however, has emerged as a topic for discussion. Theoretically, higher age could be considered as a risk factor for impaired healing due to the higher prevalence of systemic disorders or medical treatments. However, there seems to be no correlation between higher age and the risk for early implant failure.\textsuperscript{131, 163} As discussed earlier, the status of the host in general seems to play a more prominent role in the bone healing around dental implants. In Study II, younger age was correlated with higher probability for early implant failure, analyzed in groups of ten-year intervals. Subgroup analyses demonstrated that this was evident only in the group of patients who were rehabilitated late in the inclusion period, with implants with moderately rough surfaces. The specific reasons for this can be speculated. Taking into account the findings from Study III, in which matching on age was performed, it may be hypothesized that systemic disease, combined with edentulousness at younger age, may reflect a compromised general health that
influences the healing of implants also with the moderately rough surfaces, which in healthy individuals have very high survival rates and low early implant failure rates.\textsuperscript{215} Recently, it has been discussed that patients with edentulous jaws at a young age may represent a vulnerable group with higher mortality.\textsuperscript{25}

Given the information on implant surface, jaw, and age, the outcome of Study III gave further details regarding the patient and the rehabilitation process. Some of the factors that were found statistically significantly associated with higher probability for early implant failure corresponded well to previous findings within the field. Smoking, low primary stability during implant insertion, and reduced bone volume at the implant site are well known factors that can have a high impact on the risk for early implant failure.\textsuperscript{55, 57, 61, 110} The fact that the variable implants in the opposing jaw was associated with higher probability for early implant failure in the edentulous jaw needs further investigation, as well as the influence of the clinical protocol. Speculatively, this finding may be related to the fact that a completely edentulous patient with implant rehabilitations in both jaws has suffered from a more severe dental disease and may have other contributing factors for the failure of implants, compared to a patient who has one edentulous jaw.\textsuperscript{19, 208}

Healing complications after implant insertion were also found to be associated with higher probability of early implant failure in the edentulous jaw (Study III). A recent study found a higher risk for early complications after implant surgery in the presence of diabetes mellitus, including infection, hematoma, and early implant failure.\textsuperscript{210} In the current thesis, the total group of healing complications included all types of complications after surgery (i.e., pain, infection, wound dehiscence and decubital ulcers from provisional prostheses). In the univariate analyses, the subgroups wound dehiscence and decubital ulcers were more prevalent in the group of cases with early implant failure than in the group of controls ($P<0.001$). However, when included in the multivariable analysis, the subgroups were not statistically significant. Wound healing may be disturbed by smoking, which has also been found to be correlated with early implant failure (Study III). Moreover, pain after implant insertion has been associated with higher levels of pro-inflammatory cytokines and early implant failure,\textsuperscript{39} so the post-operative finding with pain, infection, or defective wound healing may be a sign of a defective osseointegration. Whether this is a result of a poorly fitting prosthesis, poor surgical technique, bad oral hygiene, or the patient’s poor healing ability remains to be understood.

In the present thesis, the healing complications did not represent information of a pre-operative anamnestic character, but the fact that it may be correlated with higher probability for early implant failure indicates that a meticulous
after-care regimen remains necessary for the possible prevention of some of the complications.

The anamnestic variable systemic disease as a total group was associated with the probability for early implant failure. Patients with systemic disease had a higher risk for early implant failure compared to patients with no systemic disease (Study III). When divided according to general health diagnoses, none of the subgroups were identified as statistically significant in the multivariable logistic regression. The prevalence of several subgroup diagnoses was higher in the total group of patients with early implant failure compared to the group without failure; however, these differences did not yield any statistically significant results when controlling for the other included variables. This finding agrees with recent studies, which displayed similar results for patients with several systemic diseases as for patients without disease, including e.g., rheumatoid arthritis, diabetes mellitus, cardiovascular disease, hypothyroidism, and osteoporosis. Other studies have demonstrated higher risk for patients with diagnoses such as cardiovascular disease or diabetes mellitus, but this finding was not demonstrated in the present study.

In Study III, the subgroup digestive organs (systemic diseases) resulted in OR 1.62 (95% CI 0.96, 2.74) (P<0.070), which is considered not significant. However, it may represent a trend that could be of interest for further analyses in the future. The digestive tract is a large system, containing different compartments including the mouth. Several disorders that predominantly affect the more distal parts of the gastro-intestinal system also manifest in the oral cavity, such as inflammatory bowel disease (Ulcerative colitis and Crohn’s disease), and celiac disease. Inflammatory bowel disease has also been related to the presence of certain bacteria, which also have been associated with other chronic inflammatory diseases (e.g., type 2 diabetes mellitus and atherosclerosis). Previously, type 2 diabetes mellitus was associated with higher risk for implant failure. Additionally, early implant failure has been associated with Crohn’s disease, gastric problems, type 1 diabetes mellitus, osteoporosis and smoking, conditions that are also correlated with bone metabolism or auto-immunity.

Furthermore, the composition of gut microbiota has been found to be associated with genetic factors and dietary intake, and it varies inter- and intra-individually. Higher diversity is generally associated with better health, and the diversity may vary according to diet, antibiotic intake or host genotype. People with pro-inflammatory diet had more tooth loss than people with anti-inflammatory diet and the findings were coupled to periodontal disease in
a recent study from the USA. Another pilot study demonstrated that a temporary change in diet resulted in lower periodontal bleeding score, indicating less inflammation. Similarly, the Western-type diet has been associated with other chronic inflammatory diseases as well as disruption of the bacterial composition of the intestine. This could also be related to the development of different allergies, as the host defense is altered with gut barrier dysfunction.

The patient’s history of allergies in general has rarely been discussed in the context of dental implant failure. When investigated, the discussions point towards a hypersensitivity reaction towards the material of the dental implant, however, the results are not conclusive. In Study III, the results indicate that the presence of allergies in general can be correlated to higher risk for early implant failure in the edentulous jaw, specifically food allergies. The findings were based on patient reported allergies/hypersensitivities or intolerances and no objective measurement on the type of allergy or hypersensitivity reaction were performed. Moreover, there are several different types of reactions involved in the different “allergies” mentioned in the present analysis. For example, celiac disease is an autoimmune disease, acting through a T helper 1 cell-mediated reaction, whereas actual allergies towards nuts or fish are immune-mediated where the humoral defense is activated by antibodies, in a type 1 hypersensitivity reaction. Furthermore, lactose intolerances can be divided into primary (non-immune, an innate lack of lactase enzyme) or secondary (due to dysbiosis) and display different reactions. Interestingly, a recent report found that penicillin allergy was associated with dental implant failure, but in the present thesis, this variable was only statistically significant in the univariate analysis, but not statistically significant when controlling for the other variables in the multivariable logistic regression (Study III).

In summary, allergies and the oral-gut connection in relation to osseointegration, and the failure of dental implants, are relatively unexplored areas and still there is more to understand. Speculatively, the presence of allergies or hypersensitivities in an edentulous patient indicates that the immune system is affected and may interfere with the osseointegration or the way the host responds to an implanted device in bone. These observations indicate that there are factors that have not previously been investigated with respect to the integration and prognosis of dental implants. Thus, further research is needed to increase the understanding of dental implant failure.

Regarding different types of medication intake, higher risk for early implant failure has been correlated with intake of SSRI and PPIs. Other studies
have failed to correlate intake of medical drugs with increased risk for implant failure, such as bisphosphonates, thyroid medication, and antihypertensive medications\textsuperscript{116, 118, 119, 124} possibly due to relatively small sample sizes in combination with the relatively low incidence of implant failure. Similarly, in the present thesis, analgesic medication other than NSAID was the only medication type that was found to be associated with higher probability of early implant failure (Study III). It is difficult to draw strong conclusions regarding intake of specific analgesic drugs, as this group consisted of several substances such as paracetamol and opioids and included both prescription drugs as well as over-the-counter-medicines. It can be speculated that use of pain-relieving medications might indicate a presence of an inflammatory disease that manifests in pain throughout the body, although systemic diagnoses of inflammatory diseases (e.g., rheumatoid arthritis) were not found significant in the present thesis. Moreover, the intake of medicines was self-reported and may not be accurately recorded when anamnestic information was transferred.

5.2.2 FACTORS RELATED TO LATE IMPLANT FAILURE - GENE EXPRESSION IN BONE / PICF

The findings from Study IV indicate an upregulation of proinflammatory markers and tissue degradation markers combined with a downregulation of osteoprotective and anti-inflammatory markers in the samples from severe bone loss compared to unaffected bone. This was observed both for bone samples from sites with severe bone loss compared to unaffected bone as well as for PICF samples from sites with severe bone loss compared to unaffected bone. The combination of these activities can resemble a T helper 1-type of reaction, with T-cell mediated inflammatory response to the implant.\textsuperscript{232} The upregulated markers RANKL, IL-17, and TNF-\(\alpha\) can be found in various bone-related conditions and the complex, multiple actions of the various cytokines need to be interpreted with caution. The IL-17 has been considered a key factor in bone destruction processes and can, in combination with TNF-\(\alpha\), promote an upregulation of osteoclastic activity by promoting production of IL-1\(\alpha\), IL-1\(\beta\), and IL-6.\textsuperscript{171} Furthermore, the upregulated RANKL in combination with downregulated OPG signals high osteoclastic bone resorptive activity.\textsuperscript{33, 40, 233} As IL-10 is an anti-inflammatory cytokine, its upregulation indicates the activation of a counteracting suppressive system.\textsuperscript{178, 234} These findings are in concert with previous findings from PICF studies, indicating different gene expression in sites with and without bone degradation.\textsuperscript{235-237} The findings in Study IV, demonstrated by the gene expression analysis, are consistent with
the clinical and radiographic findings of severe bone loss around the affected implants.

The reasons for progressive bone loss and late implant failures have been discussed and is a hot topic in parts of the dental community. Several authors have provided evidence supporting the hypothesis that bacterial adhesion to implants plays a role in the development of inflammation around the implants. However, any causal relationship has been difficult to demonstrate given that generous varieties of bacteria are constantly present in the oral cavity. Moreover, treatment of peri-implantitis is less predictable than the treatment of periodontitis, and the progression of disease has been reported in 44% of peri-implantitis cases after surgical treatment, yet, another study demonstrated lower progression of bone loss after surgical interventions. Nevertheless, it needs to be acknowledged that the bacterial milieu in the oral cavity may act in combination with other factors to affect progressive bone loss around dental implants. The bacterial effects associated with periodontitis can also be affected by the systemic condition (e.g., demonstrated in vivo that probiotics decrease periodontitis). Moreover, the combination of several general health issues called the metabolic syndrome has been associated with prevalence of peri-implantitis, further demonstrating the impact of general health on oral tissues. Other authors represent the theory of a foreign body reaction that has come to a tipping point in the equilibrium that is needed for the implant to maintain the state we refer to as osseointegration. Passing this tipping point leads to resorption of the bone surrounding the dental implant, replacing the bone with soft tissue.

The etiology behind the imbalance that leads to bone loss around the implant is multifactorial – i.e., host dependent, implant-related, and clinician influenced. Future research goals include studies regarding further understanding of the imbalance that leads to implant failures.
6 CONCLUSION

The present thesis has identified several variables that are associated with the risk for early implant failure.

I. The incidence of implant failure in a large patient group was higher for implants with turned surface compared to implants with moderately rough surface modifications, and for implants in the maxilla. Most failures were registered as early implant failures, occurring between implant insertion and first annual examination after prosthesis insertion.

II. The incidence of early implant failure in edentulous jaws was 8.6%. The probability of early implant failure in edentulous jaws was associated with type of implant surface, type of jaw (maxilla or mandible), and patient’s age at implant insertion.

III. Nine patient-related (anamnestic) and treatment-related (clinical) variables were associated with higher probability for early implant failure in edentulous jaws, when comparing a large group of patients to a matched control group without implant failure.

IV. Bone biopsies from implant sites with severe bone loss exhibited upregulated gene expression of several inflammatory and bone resorption markers compared to unaffected bone biopsies from the same patients. The results from PICF samples and bone samples from implants with bone loss were in parts corresponding.
7 FUTURE PERSPECTIVES

Dental implants are a frequently used rehabilitation method for edentulous people. Although most implants osseointegrate and remain in situ for many years, there is a still a need for more knowledge to understand the reasons for failure of dental implants.

Future studies are needed to analyze the correlation between the patient’s general health and the effect of for example systemic diseases, allergies etc., in relation to dental implant failure.

Further understanding of the correlation between different clinical conditions and dental implant failure is needed, for example the impact of severe tooth loss and healing complications.

Tissue sampling around implants needs further development to evaluate the correspondence between the status of peri-implant bone and peri-implant crevicular fluid, for the information to be used in diagnostics and evaluation of implants with severe bone loss.
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