On percutaneous implants fate and feature

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Gothenburg, Sweden, 2019
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Filip

Johan, Far och Mor
Abstract

The main objective of this thesis was to investigate skin reactions around percutaneous abutments in the facial and retroauricular regions. Secondary objectives were to investigate the number of lost extraoral implants and their co-morbidity over time, for example complications because of skin reactions due to the skin penetrating abutment. Another aim was to develop a new surgical technique to improve and facilitate soft tissue healing, explore an alternative material for the abutment to create a tighter adherence between dermis and the abutment surface and study the skin-abutment interface.

To assess skin reactions and long-term outcome for extraoral implants, a retrospective study on patients treated at the Sahlgrenska University hospital was performed and implant survival rate was estimated. This showed that a small group of 19 patients counted for 78 (55 %) out of 141 (of total 763) of the lost implants. The overall implant loss was 18 %.

A new animal model (sheep) was designed to study different types of abutments. Cylindrical and concave shaped abutments with hydroxyapatite surface material were compared with conventional cylindrical and concave titanium abutments. Samples were taken for histology, histomorphometric and qualitative analyses were carried out, showing integration between hydroxyapatite and dermis. The results suggested an advantage in using hydroxyapatite as abutment surface material. However the significance of the shape could not be determined.

Thereafter, a second study was performed to compare and further investigate the effect of abutment shape during a healing period of 4 weeks. Together, the animal studies 1 and 2 resulted in a new surgical procedure and feature of the abutment design. In sheep, the hydroxyapatite showed a firm integration with dermis.

From previous knowledge about complications with percutaneous abutments and the findings from the animal model, a cylindrical hydroxyapatite covered healing abutment was designed for human use.

This newly designed test abutment was used in a pilot study examining dermis-abutment interface after implant insertion up until the second stage surgery at 12 weeks healing. Samples were taken for
histology and histomorphometric and qualitative analyses. Results from the first patients showed that the hydroxyapatite surface induces a different interphase with the dermis compared to the titanium surface.

**Keywords:** Hydroxyapatite, bone anchored hearing aid, percutaneous, abutment, and dermal integration.
Hudgenomförande implantat - prognos och design

Populärvetenskaplig sammanfattning

**Bakgrund:** Det finns idag unika möjligheter att förankra titankomponenter i skelettet. I vissa fall är konstruktionen sådan att den behöver passera genom huden för att utgöra en förankningspunkt. Patienten kan sedan använda denna del för att koppla på en hörapparat eller en protes. Det finns dock komplikationer med benförankrade lösningar såsom; förlust av implantat och hudreaktioner av olika svårighetsgrader. Syftet med denna avhandling var att studera implantatöverlevnaden och fördelningen av implantatförluster per patient, samt att studera ett alternativt material för hudgenomföring och en alternativ kirurgisk teknik.

**Delarbete I:** Detta är en retrospektiv studie på 571 patienter (763 implantat) som behandlats med benförankrad hörapparat (BAHA) på Sahlgrenska Universitetssjukhuset 1977-2011. Studien visade att det totalt förlorades 141 (18 %) implantat under en uppföljningstid 0-32 år (medel 6.6 år). Totalt 46 patienter (8.2 %) hade någon form av implantatförlust. Anmärkningsvärt var att 78 (55 %) av implantaten förlorades i en liten grupp på 19 patienter som alla förloste två eller fler implantat.

**Delarbete II:** En djurmodell utvecklades för att studera histologiskt om det med en hudgenomförande del i hydroxyapatite istället för titan samt för att studera om det utan hudtunning och ur ett interaktionsperspektiv mellan hud och distans, fungerar att använda hydroxyapatit på den hudgenomförande distansytan istället för titan vid BAHA implantat. Totalt placerades 36 implantat i 6 st får i 1-4 veckor. Studien visade att hydroxyapatite fungerar att användas utan hudtunning och utan avvikande fynd i jämförelse med titan.

**Delarbete III:** Samma djurmodell användes för att studera hydroxyapatiten histologiskt i kontakt med hud. Totalt placerades 48 implantat i 8st får i 4 veckor. Studien visade att hydroxyapatite på distansytan interagerar med hud på ett annat sätt än titan.

**Delarbete IV:** En pilotstudie av hydroxyapatit i människa. Fyra patienter fick en hydroxyapatitdistans och en titandistans under 12 veckor i samband med annan planerad behandling för benförankrade proteser i ansiktsregionen. Studien visade att hydroxyapatitytan interagerar med hud på ett annat sätt än titan. Inga negativa kliniska effekter för patienterna noterades under studietiden.

**Slutsatser:** Rehabilitering med benförankrade hörapparater är en välfungerande behandling när indikation finns men en liten grupp patienter har problem med upprepade implantatförluster. Hydroxyapatit istället för titan på den hudgenomförande distansytan i en djurmodell leder till tätare kontakt med hud och mjukvävnad. Det finns skäl att vidare studera och utveckla hydroxyapatiten som hudgenomförande material i patienter.
List of papers

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

I. Larsson A, Tjellström A, Stalfors J

*Implant losses for the bone-anchored hearing device are more frequent in some patients*

Otology & Neurotology 2015 Feb;36(2):336-40

II. Larsson A, Wigren S, Andersson M, Ekeroth G, Flynn M, Nannmark U

*Histologic evaluation of soft tissue integration of experimental abutments for bone anchored hearing implants using surgery without soft tissue reduction*

Otology and Neurotology 2012 Oct;33(8):1445-51

III. Larsson A, Andersson M, Wigren S, Pivodic A, Flynn M, Nannmark U

*Soft Tissue Integration of Hydroxyapatite-Coated Abutments for Bone Conduction Implants*


IV. Larsson A, Eeg-Olofsson M, Dib L, Nannmark U, Rasmusson L

*Dermal integration of hydroxyapatite abutments in human - a pilot study*

In Manuscript
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## Abbreviations

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<td>BAHA</td>
<td>Bone anchored hearing aid</td>
</tr>
<tr>
<td>HA</td>
<td>Hydroxyapatite</td>
</tr>
<tr>
<td>Ti</td>
<td>Titanium</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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<tr>
<td>AC</td>
<td>Air conduction</td>
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<td>BC</td>
<td>Bone conduction</td>
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<tr>
<td>CI</td>
<td>Cochlear implant</td>
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<tr>
<td>BM</td>
<td>Basal membrane</td>
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<td>TFA</td>
<td>Transfemoral amputation</td>
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<td>HRT</td>
<td>Hormone replacement therapy</td>
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1 Introduction

1.1 Rehabilitation with skin penetrating implants

Osseointegration was initially reported by Brånemark following observations in the 1950th during a study of bone marrow circulation in rabbit, as an en passant discovery. He noticed that bone overgrew the titanium chambers and in 1969 Brånemark et al. established the term osseointegration.\(^1\) This pioneer research did not only define osseointegration, it also stated factors affecting osseointegration, materials, bone composition, necessary healing time and surgical technique. The foundation for research exploring the unifying structure of bone tissue and titanium was laid.

The current field of osseointegration research mostly focus on the dynamics and the biomechanics of titanium implants for different applications. The bone integrated implant with abutment is widely used in medicine, an anchor for prostheses, epitheses or other devices, i.e. most frequently bone anchored hearing aids (BAHA). A lot of the experiences of osseointegration are established through intraoral implants and their longevity and pattern of complications.\(^2\) Despite differences of the surrounding tissue, biomechanics and dynamics of soft tissue passage and the bone seem to share some general principles. Reports suggest that the material and shape of implants and/or abutments, constitutions of surface and stability affect the dynamics and biomechanics.\(^3, 4\)

However soft tissue interaction is of great importance as it is relevant to the longterm prognosis of osseointegration for both percutaneous and mucosal abutments.\(^5-8\) KM Holgers et al. 1987 considered that adverse skin reactions could be a reason for implant failure. Furthermore, histological evaluations of lost percutaneous implants have been performed showing patterns similar to lost retrieved intraoral implants.\(^4, 3, 11\)

The largest number of percutaneous abutments is the BAHA. Senses are important to all living organisms. Hearing is one of our five senses (vision, smell, taste, hearing and touch). In the world, 5 % (360 million) of humans experience deafness or hearing loss reported by the World Health Organisation (WHO). Some reasons for impaired hearing are genetics, birth complications, complications to infections, certain drugs, noise damage or aging. According to WHO more than 90 % of the people

Patients who have lost a limb or other body parts due to trauma or severe illness can indeed benefit from a fixed prostheses or epitheses. In 2005 it was estimated in the Unites states of America that 1.6 million people lived with some limbloss. The conventional rehabilitation using a traditional prostheses, for example a leg, often implies socket problems and difficulties in usage and affects quality of life. Hence, a method to adapt the prostheses directly to the skeleton would increase the patient benefit of treatment. This scheme of rehabilitation has been carried out since the 1990s by the Brånemark group in Sweden with success rates comparable to other percutaneous implants.

It is a treatment associated with known complications. The prognosis for percutaneous implants seems to depend on the dynamic unit of bone-implant and skin-abutment interfaces.

### 1.1.1 Osseointegration

The definition of osseointegration is based on four different viewpoints (P-I, Brånemark, *The osseointegration book: From calvarium to calcaneus*, 2005, Quintessences Berlin Chicago). Firstly, micro-, and macrobiological medical properties are defined as a functional unit of the implant without interposed scar tissue layer nor scar tissue, ligament or cartilage in between implant and bone.

Secondly, healthy bone tissue can be seen within the zone adjacent to the implant in light microscope and electron microscope.

Thirdly, no motion should be detected between the implant and the surrounding living bone and marrow at functional loading forces. Furthermore this stability should remain longterm, preferably the patients entire life. The implant should respond to loading forces the same way as if load was directly on the bone.

Last but not least, the clinical usage, providing a stable and immobile support under functional loading forces, without pain, inflammation or loosening. Osseointegration is a dynamic process and the unifying of bone cells and titanium dioxide (TiO₂) is a continuous process that can be disturbed by overload or inflammation process.
1.1.2 Bone Anchored Hearing Aid

Sound waves can reach the hearing organ (cochlea) through air conduction or bone conduction. When the cochlea is stimulated by air conduction, sound enters the ear canal and sets the tympanic membrane and the middle ear ossicles in motion, which in turn creates a wave motion of the cochlear fluids that stimulates nerve cell impulses that are transmitted to the brain stem and the auditory cortex of the brain. Hearing by bone conduction implies vibration stimulation of the skull bone where the vibrations reach and shake the cochlea which is stimulated in the same way as for air conduction.

Hearing loss due to a cochlear malfunction is commonly rehabilitated using conventional hearing aids that amplify incoming air conducted sound. With malformations of the ear canal, chronic discharging ears or hearing loss due to middle ear disease, hearing rehabilitation through bone conduction is preferred since this auditory route bypasses the ear canal and the middle ear.\(^{(20)}\)

After Prof. Brånemark had defined osseointegration as the successful adaptation of titanium to bone tissue, new possibilities arose. It opened for the possibility to anchor external materials to skeletal structures. One innovation using osseointegration was the BAHA, Fig\,1\(^{(21, 22)}\). The BAHA uses the bone conducted hearing pathway. The audio processor is attached to a percutaneous titanium implant, which is osseointegrated in the parietal bone of the skull. Sound is converted from sound waves in the air to mechanical vibrations of the skull bone, and is transmitted to the cochlea.\(^{(20-23)}\) Since 1977, the BAHA has spread all over the world.

\[\text{Figure 1 BAHA sound processor (left), BAHA abutment (right)}\]
The BAHA treatment is from a surgical and osseointegration aspect rather standardised but there are complications. As the osseointegrated implant remains in the bone, the percutaneous abutment at times causes a variety of skin complications.\textsuperscript{(15, 24, 25)}

1.1.3 Percutaneous osseointegrated craniofacial prostheses

Osseointegrated implants are also used in the head and neck region for rehabilitation of craniofacial defects, Fig 2.\textsuperscript{(22, 26-28)}

Implant retained prostheses contribute to an increased stability, safety and satisfaction, compared to traditional adhesive solutions.\textsuperscript{(29)} Success rates for non-irradiated patients are 95 \% and in irradiated patients 80 \%.\textsuperscript{(27)}

![Figure 2: Ear prosthesis/epithesis (left), abutment bar construction attachment with skin reaction (right)](image)

1.1.4 Percutaneous osseointegrated prostheses for transfemoral amputations

Another application is the possibility to anchor limb prostheses directly to the skeleton via osseointegration. More than 200 patients have been treated this way in Sweden.\textsuperscript{(14, 30)} The rehabilitation gives the patients an increased ability of movement and tactile perception.\textsuperscript{(31, 32)}

But as with other percutaneous solutions the treatment is jeopardised by complications such as skin infections. Soft tissue infections and other
problems are reported to be up to 47%. Studies of different abutment designs have been published without showing improvement of skin conditions. In fact, some cases with a rough titanium surface show even higher frequencies of infection, due to a more readily formation of biofilm. Shin et al. 1997 found that glassy carbon and porous HA did not affect the soft tissue. However, studies with sheep and porous titanium showed favourable results for the soft tissue outcome. Also animal trials with flange design to improve the percutaneous passage have been successful.

1.2 Skin

Our largest organ is our envelope - skin (integument). It will shield us from the external environment but also function as a tactile organ. Skin together with mucosa is continuous with the exceptions of nails, teeth and eyes. The skin organ is made up of layers, and thickness varies from 1.5-4 mm. The most superficial layer, named epidermis, is thick epithelium; dermis lies below the epidermis and is composed of fibrous connective tissue. Innermost lies subcutis or hypodermis which is a fatty layer of adipose tissue not truly a part of the skin but of significance to the cutaneous passage of an implant abutment.

In the epidermis there are mainly four cell types; keratinocytes, melanocytes, Merkel cells and Langerhans cells. As their name indicate keratinocytes produce keratin, a structural protein that will give the skin protective entities. Apart from the mechanical properties, keratinocytes produce antimicrobial substances and neutralising enzymes that will incapacitate harmful chemicals. Keratinocytes are continuously regenerated and migrate upwards from the basal membrane. They are connected by anchor proteins so called desmosomes. Skin surface consists merely of dead keratinocytes and is renewed within 4-6 weeks. Thickness of the epidermis is proportional to the exposure of friction.

Epidermis divides into five layers at the most. The layers have their different characteristics and cell composition. The deepest skin layer named basal membrane (stratum basale) is a single row of cells with mitotic nuclei continuously undergoing cell division. Every 4th-10th cell in the basal membrane is a melanocyte responsible of melanin production, which gives us our pigment. It is enclosed into small granules that are passed outwards to the keratinocytes. In between these keratinocytes
there are Merkel cells with associated sensory nerve endings that respond to touch.

Next layer, stratum spinosum, is characterised by few cell divisions and keratinocytes tightly joined together by desmosomes. Dispersed throughout the layer are Langerhans cells, stellar formed type of dendritic cells that are part of our immune system.

Stratum granulosum consists of layers of flattened keratinocytes. Lamellate granules containing a hydrophobic glycolipid are produced by the cells and deposited extracellularly adding a waterproof character to the layer. The cell walls in the stratum granulosum are thicker, and together with the richness of tonofilament it resists tears and shreds.

Second outmost is the stratum lucidum, a layer with a mixed character of the adjacent layers.

The surface layer, stratum corneum, will be of different thickness depending on the individual and where the skin is on the body. There is no cell division and all keratinocytes are flat and dead. They are joined by the keratohyalin from granules produced in deeper layers, giving protection from physical damage together with hydrophobic glycolipid. This is our protective shield towards water loss and rinse.\(^{(37)}\)

1.3 Surgical procedure

When discovered that osseointegrated implants could transmit sound waves and bear weight load, implementation of BAHA and transfemoral amputation (TFA) prostheses treatment started. The procedure is surgical and will disrupt the skin barrier with all above mentioned components and layers of skin down to the periosteum.

Throughout time, different methods for the BAHA surgical procedure have been used however all creating sharp wound edges adjacent to the implant abutment.\(^{(38, 39)}\) Today, implant insertion with percutaneous passage is performed in a one-stage procedure. Earlier, the implant was left for osseointegration and at a second-stage procedure, the percutaneous abutment was connected.

A skin flap has traditionally been lifted behind the ear, punched and folded over the abutment. There have also been different traditions of how to raise the flap, by a semi-circular or linear incision. There are several methods to reduce the skin in thickness and to remove hair follicles with or without a dermatome.\(^{(40, 41)}\) Hence, there is no consensus internationally on gold standard procedure. The skin thinning method is
now more or less abandoned. Instead the complete skin and soft tissue is preserved, either using a linear incision or a simple skin punch down to bone where the implant with the attached abutment is screwed firmly in the bone.\textsuperscript{(42-46)}

Children are often treated at a young age and mostly through a two-stage procedure. This is to avoid trauma in the early post implant stage. Loading can, according to a consensus report from 2005, be from 3 weeks.\textsuperscript{(47)}

For TFA treatment, the implant will be inserted at stage 1 and remain unloaded. After approximately 6 months healing period stage 2 is performed. Muscle flaps are adjusted and skin is trimmed with thinning, removal of subcutaneous fat and hair follicles. The abutment will be press-fitted firmly onto the implant and load bearing is strictly regulated and increased over the first 2-12 weeks after stage 2.\textsuperscript{(14,48)}

1.4 Surgical complications

At all times post surgery, inflammation occurs with typical features of rubor (rush), tumor (swelling) calor (heat/flush), dolor (pain), functio laesa (loss of function) and in addition hematom\-a. Wound infections of varying degree can occur. Features of infection are typically more intense and can cause spontaneous implant loss or need for local and/or oral antibiotics. It can be necessary to remove an implant and abutment surrounded with persistent skin reaction.\textsuperscript{(17,33)}

Necrosis of skin is one of the most severe complications to BAHA surgery. It occurs, when thinning the skin, which disrupts the blood circulation and diffusion from submerging dermal layer.\textsuperscript{(49-51)}

Numbness and loss of sensation can also be a lasting complication for patients, caused by trauma of small nerves in the skin when thinning the flap. In literature there are cases of local pain syndrome most likely caused by failed nerve healing.\textsuperscript{(16,52)}

Along with skin thinning, hair follicles are removed and alopecia in the region of the abutment is to some individuals unaesthetic.

1.5 Skin complications

Skin complications in BAHA and FTA treatment are common and reported frequently.\textsuperscript{(53, 54)} Retrospective studies have been made on complications of BAHA and need for skin corrections.\textsuperscript{(15, 55)} Skin
complications are referred to as overgrowth of skin, dermatitis or postoperative flap complications.

The etiology of skin reactions is not fully understood. In 1984, von Recum et al. addressed different modes of the skin/implant junction and mechanisms of epidermal healing.\(^{56}\) von Recum et al. postulated a process resulting in failure; implant loss, by epidermal encapsulation. This epidermal proliferation and migration seeking to heal the wound eventually undermined the percutaneous device, much like a foreign body reaction. In theory, this might cause skin overgrowth or skin downgrowth along the abutment and thereby jeopardising the osseointegration.

Holgers et al. 1999, stated that microbiological conditions from human percutaneous titanium implants in the head and neck region promote hydrophilic cell surfaces, which in turn make the infections around titanium implant curable by local treatment.\(^{57}\) In orthopaedics different antibacterial coatings on fracture fixation pins have been tried showing lower rates of tract infection.\(^{58}\) The findings that antibacterial agents limit skin reactions suggest that bacteria have an effect on the percutaneous passage.\(^{59, 62}\) However, it is not clear whether the skin reaction is a result of bacteria or if the skin reaction promotes bacterial colonisation secondarily. It has also been argued that the property between the skin and titanium is a factor contributing to skin reactions, since the abutment of titanium does not adhere to the dermis. Studies have shown a layer of epidermal tissue between the skin and metal.\(^{63, 64}\)

Jansen et al. (1994), demonstrated that less motion of skin around the abutment enhances the soft tissue condition.\(^{65}\) They suggest less complications, the thinner the skin, due to less mobility of the interface of the abutment. This is also considered for intraoral implants, where keratinised mucosa adjacent to the abutment could favour the prognosis of implant survival.\(^{66}\) In 2008, Wolf et al. presented new data on a simplified BAHA surgical procedure but still with skin reduction.\(^{67}\) Reports from 2010 describe that skin complications can occur likewise with skin reduction using dermatom or scapel. Recent reports suggest that the linear incision without thinning the skin at all show even less complications, hence the minimal invasive surgical BAHA procedure is of large benefit for the patient outcome.\(^{15, 24, 68, 69}\)

Hobson et al. 2010, also reported for BAHA, that there is an increased risk of skin complications seen among patients with Downs syndrome.\(^{70}\) However literature lacks more data on, if some patient groups are more susceptible for adverse skin reactions than others. It is not further studied.
if these complications are concentrated to any certain group of patients, i.e. patients with congenital malformations or syndromes. Hobson et al. 2010, also reported that overall complications (soft tissue overgrowth, skin infection, abutment and fixture dislodgement, trauma, skull paraesthesia, persistent pain at abutment site, failure to osseointegrate) were 23.9 % and revision was performed in 12.1 % in their study. This correlates to previous studies that report a range between 8-59 % with revision rates of 5-42 %.\(^{(15)}\)

In short term skin complications mimic those of inflammation post surgery. Over time skin reactions have been divided into different grades 1-4 according to KM Holgers index, where 1 is least and 4 most affected skin and even implant loosening.\(^{(71, 72)}\) It is not however a fact that all skin reactions will lead to loosening of the implant.\(^{(55)}\)

Skin overgrowth is a common complication.\(^{(73, 74)}\) The extent of overgrowth and under which timespan it develops vary in studies, ranging from partial cover of abutment to full overlap and from post operative healing 3 months and up to 2 years.

### 1.4.1 Treatment of skin complications

Patients are always recommended daily hygienic care such as wash or rinse.\(^{(55, 60)}\) Local treatment with topical anti-flogistics and antibiotics is always used immediately post operative to avoid local reactions but can also cure symptoms later on.\(^{(60)}\) Another treatment option might also be corticosteroid injections.\(^{(73)}\)

Sometimes non-surgical treatment is not enough. Overgrowth of skin could be caused by chronic inflammation. However, it could also occur if an abutment is out of use for a longer period. Hence patients are advised to use their sound processor as consistently as possible. Invasive treatment such as reduction of skin overgrowth with trimming or switching to a longer abutment can then become necessary.\(^{(5, 46, 74-76)}\)

Adverse sensory conditions concerning pain are rare but hard to treat successfully and can at times be very disturbing for the patient.\(^{(16)}\)
1.5 Abutment Material

Traditionally, titanium has been used for both implant and abutment. In odontology implant and abutment material surfaces are widely investigated and explored.\(^{(77)}\) For intraoral abutments the trend has changed from titanium to ceramics for their supposed biocompatibility.\(^{(78)}\) Percutaneous abutments are far less common and hence there is a sparse number of studies on the material use. Nevertheless different porosity of titanium coatings has been studied.\(^{(35, 79, 80)}\) Literature reports different results from these studies suggesting there might be alternatives to pure titanium to favour connection to skin.\(^{(81, 82)}\)

1.5.1 Hydroxyapatite

\[ \text{Ca}_{10} \text{PO}_{4}(\text{OH})_2 \] calcium phosphate ceramic named hydroxyapatite is a naturally occurring inorganic compound found most commonly in cortical bone.\(^{(83)}\) In our bodies hydroxyapatite can occur as highly crystalline or amorphous as it is continuously turnovered by the calcium haemostsis. Synthetic hydroxyapatite resembles the natural bioceramic well but is not as easily resorbed.\(^{(84)}\)

In 1987, Aoki et al. reported on hydroxyapatite sintered abutments in an animal model showing that the material was closely connected with the skin and that epidermal downgrowth of epidermis was limited to 1mm. After 3-17 months a fibrous capsule was formed with characteristics of periosteal tissue.\(^{(85)}\) Some years after this in 1994 Thomas et al. wrote a review “Hydroxyapatite coatings” with the focus on integration of hydroxyapatite in bone.\(^{(83)}\) They stated that hydroxyapatite forms a direct bond to living bone in orthopaedic use.\(^{(86-89)}\)

Hydroxyapatite can be applied on a surface through plasma spray, a process that includes high temperatures. The compound can therefore change chemically and structurally. However, by means of x-ray diffraction (XDR) and FTIR spectroscopy characteristics can be defined.\(^{(83, 90, 91)}\) Ca/P molar ratio of 1.67 is aimed for to simulate the biological hydroxyapatite in living bone.\(^{(92)}\)
2 Aims

The general aim for my thesis was to study the percutaneous abutment and its interaction with soft tissues. Specific aims for this thesis were to:

1) Investigate skin reactions, implant complications and other potential co-morbidities.

2) Investigate long-term survival rate of BAHA implants.

3) Develop new surgical techniques to improve and facilitate the soft tissue outcome, explore an alternative material for the abutment to create a tighter adherence between dermis and the abutment surface.

4) Describe the characteristics of the interfacial soft tissue next to the abutment.
3 Material and Methods

3.1 Animal model

3.1.1 Animals
Animal experiments in paper II and III were approved by the Regional Ethical Committee for Laboratory Animals at Gothenburg University and carried out within the international guidelines for ethical use of animals. The black female sheep were selected to be suitable because of their skull size and anatomy. It was a nouveau animal model and study II was an animal model trial as well. For both study II and III female black sheep of average 50 kg were used and spent 2 weeks prior to the surgery in the laboratory housing for acclimatisation. The sheep were kept 2-3 per stable with ad libitum access to hay, food and water.

3.1.2 Surgery
After acclimatisation, the sheep underwent surgery during general anaesthetics i.v (PropoVet 0.2 ml/kg) after sedation i.m with Dextromit 0.015 mg/kg (Orion Pharma, Sollentuna, Sweden). After induction animals were intubated and kept at a minimal alveolar concentration 1.5 of isoflurane (Isoba; Intervet, Sollentuna, Sweden). All vital parameters were kept stable. To reverse Dextromit animals were given Antisedan 0.075mg/kg (Orion Pharma, Sollentuna, Sweden). To maintain analgesia after surgery Temgesic 0.02 mg/kg was given. Desinfection with iodine solution was carried out as well as trimming of hair. 5 ml of 0.5 % Marcain (Astra Zeneca, Södertälje, Sweden) was locally administrated at each surgical site. A 4- to 6 cm incision was placed behind and above the orbital rim and just in front of the ear bilaterally, Fig3. Elevation of periosteal flap and insertion of 4 mm implants 3 on each side (Cochlear Baha™, BI300) approximately 5-10 mm apart with a premounted 9mm abutment (Cochlear Baha™, BA300) were performed at a torque of 25
Ncm. Stability of the implant was verified using Ostell ISQ instrument Smart Peg type 55 (Ostell, Gothenburg, Sweden). In study II, four different abutment configurations were used. According to a predefined rotation scheme each animal received 1 or 2 of each abutment types: 1) standard titanium abutment (Cochlear Baha\textsuperscript{TM}, BA300 Abutment), 2) standard tintanium Baha abutment coated with hydroxyapatite, 3) concave titanium abutment and 4) concave hydroxyapatite coated abutment. In study III type 1 and 4 were used.

![Figure 3 Implant localisation in sheep](image)

For both study II and III. All sheep had 6 implants installed after a randomized protocol.

### 3.2 Human model

#### 3.2.1 Patients

Patients with traumatic loss or due to illness and were planned for craniofacial implants at the Universidade Paulista (UNIP) were included in a pilot study after ethical approval by the University board, according to Brazilian legislation. Patient consent was obtained for the option of having healing abutment with hydroxyapatite (HA) (Test Abutment) as well as abutments of titanium (Ti) (Control Abutment). Patients’ treatment plan was not altered by the study. So far only 4 patients are included in the pilot study.
3.2.2 Material

At least one Ti and one HA abutment all shaped as cylinders were used in each patient. Test abutments were made of titan grade 4, 6 mm high with a diameter of 3.2 mm, produced by KTMAB, Fig 4. HA abutments were plasma sprayed with 55-60 um-thick, 63 christallinity and Ca/p molar ratio of 1.67 HA by Cambioceramics (Zernikedreef Leiden Netherlands), similar to commercially used HA abutments, Cochlear™ Baha® DermaLock™ Abutment (BA400). As HA will change charateristics when heated, Co-60 Gamma irradiation was used to obtain sterility (BBF Sterilisationssservice GmbH Kernen Germany).

Figure 4 Healing abutment design
Design of the healing test/control abutment prototype used in study IV.
3.2.3 Surgery

During local anaesthesia (LA), insertion was performed according to protocol. Each patient received at minimum one test and control abutment, placed according to their therapeutic need, Fig5.

Surgical sites were irrigated with saline solution and the skin edges repositioned. No soft tissue reduction was performed. To ensure good adaptation between abutment and surrounding skin, a biopsy punch was used in 2 cases to adjust skin edges before suturing the soft tissue around abutments with none-resorbable sutures (Ethilon 4/0, Ethicon Johnsson&Johnsson). In one case implants were positioned outside the insicion line and the abutments had to be tunnelled through punched holes in the skin. Wounds were dressed with gauze and Terracortil Polymyxin B, Pfizer®.

After surgery patients were discharged from the hospital with prescribed per os analgesics (5-10 mg Morphine, Paracetamol 1 g x4) for 14 days and antibiotics (Flucloxacillin 1 g x3) for 7 days. Removal of sutures and undressing were performed by hospital staff after 2 weeks.

Time to second surgery was between 8-12 weeks depending on surgeons decision. Local anaesthesia was administered via injection of 5 ml Marcaine 0.5 %, and a 4 mm ø punch biopsy was used to collect the sample consisting of the abutment and the adjacent tissue. Samples were immediately fixated in 4 % paraformaldehyde. From each patient one test HA abutment and one control titanium abutment were taken.

Figure 5 Implant localisation (auricular)
On the left hand side a test abutment with hydroxyapatit coating (greyish) and to the right hand side control abutment of titanium.
3.3 Methods related to the specific papers included in this thesis

**Paper I**

Data registered retrospectively were; number of implants, sex, age, therapeutic diagnosis, side of implantation, length of implant, one or two stage surgery, date of failure at the loss of implant, cause of failure grouped into; loss due to trauma=1, infection or lack of osseointegration=2, no beneficial sound function=3, removal of abutment but implant still in patient=4, removal because associated pain=5.

Patients who underwent a standard two-stage procedure had a semilunar incision and a 4 months healing period prior to a second procedure with abutment attachment and loading at time of soft tissue healing. Patients who underwent a single stage procedure were treated with semilunar or linear incision and received an abutment on day of surgery but waited 6-12 weeks before loading.

**Paper II**

Thirty-six Baha implants and abutments were inserted in the skull of six skeletally mature female black sheep without performing soft tissue reduction. Four different abutments were used. Healing times of one, two and four weeks were used (two animals per time point). Samples were analyzed using descriptive histology and morphometric measurements Fig 6.

![Histological measurements](image)

**Figure 6 Histomorphometric measurements**
Schematic illustration of pocket depth (PD), epidermal downgrowth (EDG)
**Paper III**

Forty-eight implants and abutments were inserted in the skull of six skeletally mature female black sheep without performing soft tissue reduction. Two different types of abutments (test and control) were inserted in the skull parietal part of eight sheep. Test abutments had a hydroxyapatite-coated surface and a concave shape. Conventional titanium abutments were used as controls. A follow-up time of 4 weeks was used. Histomorphometric analyses of test and control samples were analyzed, and morphometric results were compared.

**Paper IV**

4 patients have so far been included in the pilot study. Two different abutments were used. Average healing time of 12 weeks. Samples were analyzed using descriptive histology and morphometric measurements.

### 3.4 Histology

**Paper II, III, IV**

Histomorphometric analysis was in studies II, III carried out via photomicrographs and analysed by Easy Image 3000 (Tekno Optik AB Gothenburg Sweden) software. In study IV NIS-Elements D 3.2 64-bit software (Nikon Metrology, SARL Lises France) was used. Light microscope images were in all studies obtained with a Nikon DS-Ri1 camera (Tekno Optik AB and Nikon Instruments Inc Meville, U.S.A).

### 3.5 Statistical Analyses

**Paper I**

For this retrospective study, descriptive data, frequencies tables were computed. Then also a Kaplan-Meier analysis was used to estimate the long-term survival rate of the titanium implants. Survival rate was estimated for the total cohort of installed implants, as well as for only the
first implant. Kaplan Meier analysis was performed by an independent bio-statistician.

**Paper II**

For this first animal study Wilcoxon’s signed ranked test for statistical analysis of differences in histomorphometric parameters between abutment types was used. In the comparisons all test samples were included irrespective of healing time. A 5 % significance level was adopted. Statistical analyses were performed by an independent bio-statistician.

**Paper III**

This second experimental study included more animals than in paper II and we opted for a mixed model analysis with implant and animal as fixed effects. Hence, adjustment of *within animal correlation* was possible and used for comparisons between test and control abutments. A mean value of measurements performed at the left and right side of each abutment was used in the analysis; implant loss and nonvalid data due to artifacts were considered as missing data and were not imputed. To determine a 5 % significance level we used a Two-sided significance test. Statistical analyses were performed by an independent bio-statistician.

**Paper IV**

For the human pilot study we decided for a qualitative histomorphometric analysis and only a descriptive statistical analysis of differences in histomorphometric parameters between abutment types. In the comparisons all test samples were included irrespective of sample quality.
4 Results

4.1 Paper I

Baha is a successful treatment however a small group of individuals represent repetitive failures. At the ENT department Sahlgrenska University hospital patients have had great possibility of rehabilitation with osseointegrated implants to conduct sound since 1977, Fig 7.

In our material that spans over the longest time in the world at time of the publication, we found that a small group of individuals had an increased risk of implant loss. Out of 571 patients treated and 763 implants inserted, failure was seen in 46 (8.2 %) patients and 109 (14 %) implants were lost. Only 21 (3 %) implants were lost due to loss of osseointegration.

As the implants were inserted over a long period of time, different surgical techniques were used. The different surgical technique parameter was not studied in this paper. Our study suggests that there may be patients that are more prone to lose implants and that 4 mm implants have a higher survival rate than 3 mm implants 74 % vs 56 %) at 10 yrs.

![Cumulative Number of implants 1977-2011](image)

**Figure 7** Number of Baha implants 1977-2011 at Sahlgrenska ENT Department
4.2 Paper II

The results from this experimental study showed that surgery with thinning of the skin not is necessary when using hydroxyapatite abutments.

Histomorphometric analysis of the samples showed that tissues around all abutments had limited or no sign of inflammation. The hydroxyapatite abutments also showed signs of adherence to dermis compared to the titanium abutments that developed an epidermal downgrowth. Hydroxyapatite creates adherence to dermis in sheep. The concave hydroxyapatite abutment showed a tendency to have less epidermal downgrowth (1.53 mm vs 1.12 mm \( p = 0.063 \)) and pocket formation compared standard abutment shape (1.26 mm vs 0.83 mm \( p = 0.031 \)), Fig 8.

![Pocket depth (mm)](image)

Figure 8 Histomorphometric measurements (all healing times) (mm). A) Standard titanium Baha® abutment, B) Standard titanium Baha® abutment coated with hydroxyapatite, C) Concave titanium abutment, D) Concave titanium abutment coated with hydroxyapatite

4.3 Paper III

Histomorphometric analysis showed a statistically significant difference in mean pocket depth between the hydroxyapatite concave shaped abutment and standard titanium abutment (0.4 vs 1.6 mm \( p = 0.0013 \)). Epidermal down growth was also measured with a difference of 0.6 vs 2.0 mm (\( p = 0.0003 \)).
4.4 Paper IV

Samples from 4 patients show an interphase between HA and dermis. All abutments showed limited or no signs of inflammation. Two patients’ samples had major artefacts. A limitation in this study is the sample retrieval procedure and embedding of the samples. The artefacts may affect the histomorphometric and qualitative analyses.
5 Discussion

A successful treatment with osseointegrated implants relies on a biological tolerability.\(^{10, 18, 19, 93}\) Loosening of implants can occur for numerous reasons and skin reactions might not correlate to implant loss, however, it might cause great inconvenience for the patient.\(^{4, 5, 55, 94}\)

The effects on the soft tissue may, or may not, correlate to ongoing bone pathology causing implant loss.\(^{55}\) In light of the results from the first paper in this thesis, it seems like a small number of patients are prone to loose implants. A small group of 19 patients counted for 78 (55 \%) out of 141 (of total 763) of the lost implants, and only 49 (8.2 \%) of the patients lost one or more implants. This observation is in accordance with studies on intra oral implants by J Derks et al. 2015, where 33 \% of lost implants were counted for in a small group of 19 patients losing 2 or more implants.\(^{95}\)

Individual factors associated with oral implant failure have been studied and Alsaadi, et al. in 2007 reported that patients with Mb Crohn, diabetes type I and patients treated with HRT (homone replacement therapy) had more complications and failures. Smokers have a higher odds ratio of early implant loss than non-smokers.\(^{95-97}\)

In the retrospective study (Paper I) data for the subcohort of implant losses showed that males lost more implants and that 3 mm implant failed more often than 4 mm implants. Gender was not assessed in the review by Esposito et al. 1998 for intraoral implants, only age and genetics. Gender related differences in bone biology between males and females mostly occur postmenopausal and are more related to the large bones such a wrist, femur and spine.

In trials with shorter intraoral implants Rossi et al. 2016, showed that 6mm implants work well over time but are sometimes affected by marginal bone loss in the form of micro fractures.\(^{98}\)

Moreover, in a consensus report 2018 on dental implants, the only contraindication for implant rehabilitation was in patients with ongoing high dose antiresorptive treatment due to cancer disease. These patients are designated to a high failure risk.\(^{99}\)
Pattern and etiopathogenesis of implant loss are multifactorial, and even recently described as an immunological reaction to a foreign body. \(^{(10, 100)}\)

Reactions against foreign bodies are inevitable but seem to differ depending on material and site. Osseointegrated implants have been widely explored over time but it might be that the peri-implant condition not at all is a disease as previously stated. \(^{(101)}\)

In 1994 K-M Holgers presented a dissertation on the soft tissue reactions around titanium implants penetrating the skin. It has laid the foundation for scoring of skin reactions and tissue characteristics adjacent to titanium abutments. Holgers stated that titanium creates no delayed hypersensitivity, nor does it create any epithelial attachment and that the soft tissue is loosely adaptive to the abutment. The loose character of the peri-abutment soft tissue has been historically considered to be a reason for complications. \(^{(56, 102)}\) Therefore thinning of the skin in various ways has been a standard method. For patients undergoing surgery for bone anchored hearing aids this procedure compromises the esthetics and can also cause numbness in the peri-abutment area. In 2014, Hultkrantz et al. presented a 5 year follow-up study with bone anchored hearing device implantation without tissue reduction showing that this technique had fewer clinical complications than flap and dermatome techniques. \(^{(46)}\) In 2016 Roplekar et al. performed similar surgery and noted less clinical complications using a linear incision with tissue preservation. \(^{(103)}\) Another technique towards less invasive surgical technique was also used by Gordon et al. 2015 \(^{(39)}\) They suggested to use a punch biopsy of the skin showing even less complications than the linear incision preserving the skin. \(^{(104)}\) In our second and third paper we developed an animal model to explore the histology of the skin adjacent to percutaneous abutment using skin preservation linear incision. The histological results from this material agree with the former studies that a percutaneous passage of bone anchored hearing aid can be achieved without thinning the skin.

The animal model also showed that HA could be of advantage for percutaneous abutments and this correlates to earlier animal models. \(^{(105)}\) HA has widely been studied for its osteoconductive properties, however, less extensive for its dermal interactions. In a work by Aoki et al. 1987, HA showed limited tendency to capsule formation around percutaneous devices. \(^{(85)}\) Twenty years later, DeJong et al. tried hydroxyapatite/chlorhexidine coating in external fixator pins and had less infections compared to stainless steel and titanium. \(^{(106)}\) Skin irritation or infection are parameters that often represents clinical status of an percutaneous
abutment. However, it is not certain that soft tissue reactions lead to implant loss\textsuperscript{(55, 63, 71, 100, 107)}

HA interaction with human skin has also recently been studied by van Hoof et al. and Kapsokalyvas et al. Both authors suggested that HA can interact with dermis in a way not seen with titanium. Kapsokalyvas group also presented histology results of the periabutment soft tissue with immunochemistry and characterisation of hemidesmosomes and dermal collagen. These findings are, however, based upon few cases.

Case studies are unreliable to draw general conclusions from but are however necessary to further develop the biomaterials.

The last paper is in manuscript as a case study and further studies will hopefully result in a larger set of data and improved knowledge of percutaneous HA abutments characteristics in human. The protocol to use a healing abutment can give an opportunity to study histology in an unbiased cohort of patients, excluding patients that have a clinical indication for abutment change or removal for other reasons. This human model could, however, be criticised since the healing time will not extend 12 weeks and one could argue that at least 12 months follow-up time would represent a final outcome. Consensus from 2005 on healing times for bone anchored hearing aid implants is 4-6 weeks and for other craniofacial implants there is no standard but in several studies healing times of 3-6 months are reported.\textsuperscript{(27, 47, 110)}

Parameters and effects of HA plasma sprayed on titanium as in study 4, only present the effects of a narrow range of crystallinity 63\% as well as thickness mean 75 um. Jeyapalina et al. 2012 showed that a porous titanium surface with the Ra(surface roughness)=1.7 + - 0.1 ug also gives an improved subdermal barrier. This analysis was not performed on HA abutments as the crystallinity is a quality standard for bioceramics. Therefore the comparability is limited along with the difference in lipophilicity and hydrophilicity.

The chemical interactions of HA and skin are not studied in this thesis but for HA and osteogenesis, Nakazawa et al. 2017 presented a cellculture study. They noted that HA when exposed to cellcultures changed from hydrophobic to a hydrophilic surface and that titanium HA coated surface increased the osteoblastic proliferation without losing other chemical features.

One might say that HA merely changes the interaction with skin but it could not be said that this will affect the longterm outcome for the patient. There are few studies on percutaneous abutments with HA but several for HA on other medical devices such as dental implants and hip-
and knee prostheses. Biomaterials need to be thoroughly tested in animal models as well as clinical trials before used as standard in surgical procedures.

Even though study I is based upon a large data set it still is a retrospective study with limitations. Sahlgrenska ENT clinic was from the beginning a referral center for all bone anchored hearing aid treatments and therefore the mean follow-up time drops in comparison to international studies form Nijmegen 2008, 2013, Manchester 2009 and Birmingham 1996, 2002. Hence the statistical method (Kapland-Meier analysis) had to avoid excluding patients with short follow-up time. This statistical method will only give an estimate (Life table) on the survival rate of an implant instead of the actual time of survival.

In study II and III sheep were used to test biocompatibility of HA as well as surgical protocol. Pendegrass et al. 2006 used deer in a study of the skin barrier around percutaneous abutments, however animals cannot fully reflect the situation in humans. Animals might be less sensitive for percutaneous passage or surgical technique. It could also be that these animals have a higher immunological tolerability to foreign bodies by evolution than humans. Animal studies will always just be a way to rule out truly adverse reactions.

The histological preparations of samples in study II, III and IV are well documented and used as standard methods for studying osseointegration along implants. However, artifacts in the samples might occur. There can be an alternation in the peri-abutment tissue when samples are taken from the animals or patients. Disintegration of the soft tissue from the abutment can also occur during fixation as well as shrinkage during the dehydration and embedding. Hence, results from the histomorphometrical analyses in study II and III might, have been affected. However, very few artefacts were recorded. Also, histological analyses of HA vs titanium abutments can never be blinded, due to the totally different surface appearances in the microscope.
6 Conclusions

1) BAHA is generally a successful treatment but a small group of individuals represent repetitive failures.

2) Life table analysis showed long-term survival rate of 74 % for 4 mm BAHA implants and 56 % for 3 mm BAHA implants.

3) The surgical procedure with thinning the skin is not necessary using hydroxyapatite abutments.

4) Hydroxyapatite create adherence to dermis.
7 Future Perspective

It is so fruitful to encourage the crossfield research with medical and dental experiences of biomaterials and their usage as seen in the study by Albrektsson et al 2019 on foreign body reactions on dental implants and hip prostheses. In the field of biomaterial the collaboration of scientists with different focus is common.

For the future clinicians could also benefit from looking sideways, even though the biomaterial might be used in a different part of the body. A lot of the biological interactions can be similar and maybe even more similar than animal testing. It can hopefully be possible to do more testing on a cellular level with different biotech models/chambers resembling the human in an adequate way. Making animal and human trials unnecessary.

The future for BAHA has already proceeded a lot since these studies were performed and for patients with a need of BC hearing aid there are transcutaneous solutions today, without need for skin penetration.

HA remains an interesting biomaterial that is widely used for different applications today in medicine and hopes are that the development of HA applications can come to further progress in soft tissue interaction.
8 Acknowledgement

My sincere gratitude to all who have taken part and contributed to this thesis. A special thank to:

Professor Lars Rasmusson, my supervisor for making this doctoral thesis possible by taking me on as a student at the Department of Oral and Maxillofacial surgery. You inspire and support a great research climate.

Associate Professor Ulf Nannmark, my supervisor who from the very first semester in Dentistry program supported me with cheers and challenges. A friend in all aspects of life. Thank you Ulf, I am so glad to have you in my life.

Associate Professor Måns Eeg-Olofsson, my supervisor for all input and guiding in the ENT-field. You keep the balance of thrive and sensibility.

Associate Professor Anders Tjellström, the founder of BAHA, great clinician and researcher, for giving me a perspective of the BAHA evolution.

All My co-authors; Stina Wigren, Marcus Andersson, Mark Flynn, Joacim Stalfors. Thank you, for taking me on the A-team!

Luciano Dib for great collaboration and hospitality during my visit in Brazil.

Gösta Granström for supporting me and introducing me to the research field of extraoral implants.

Gunnar Ekeroth and Aldina Pivodic, for all dazzling statistics and for your great input and understanding of the subject.

To the staff at HistoCenter, Petra and Carina at the Department of Prosthodontics and Dental Materials Science for all the work with preparing the samples. Without you I would not have published these papers.
To the staff at the Lundberg lab, you make a great difference for all animals that you house.

Professor Anders Lindahl for your encourage in my very first research years, you got me hooked on exploring new research fields.

Yvonne och Gunnel at the former Electron Microscope Unit for inspiring me and teaching me all basics in preparations of samples and immunohistochemistry.

Current Head of Specialistkliniken för Käk kirurgi Sanjiv Karangaraja and former Head and Tutor of the Specialist training program Mats Wallström for giving time off clinic to do research and all staff at the clinic for good support.

Head of Surgery and Orthopedics at Alingsås Hospital, Henrik Jonsson for enabling clinical work and research time and all colleges at the hospital for good support.

To all dear friends; Jenny, Bia, Anna, Reza, Anna-Lena, Lisa, Jennie, Martin for cheers, encouragement, love and all other things “just not research”.

My dear mother, father for years of endless support and love for me and my son.

My better half Johan, you are my soulmate.

Filip you are my universe.
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