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BIOLOGICAL RESPONSE TO ADDITIVELY MANUFACTURED SUBPERIOSTEAL JAW IMPLANTS AND RESEARCH TO PROMOTE FURTHER BIOFUNCTIONALIZATION

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Samenvatting

Eén van de meest gebruikte opties om retentie van een uitneembare prothese te verbeteren is door middel van enossale implantaten. Echter, bij gevorderde resorptie kan het botniveau zodanig slinken dat er geen mogelijkheid meer is om deze “klassieke” implantaten te plaatsen. Orale rehabilitatie van de ernstig atrofische maxilla (Cawood V-VIII) vormt dan ook een grote uitdaging voor menig chirurg en tandarts. Verschillende (pre)prothetische (chirurgische) technieken bestaan om de retentie van een uitneembare prothese te verhogen maar elk van deze technieken heeft hun beperkingen en ze kunnen geassocieerd zijn met aanzienlijke nadelen voor de patiënt.

Dahl introduceerde het eerste subperiostale implantaat rond 1940 en hoewel er langetermijnoverleving van conventionele subperiostale implantaten beschreven is, werden deze implantaten minder en minder gebruikt vanaf de jaren zestig. Heden ervaren deze subperiostale implantaten een opleving in populariteit. Vooruitgang in technologie en materialen, de opkomst van de moderne tandheelkunde en betere tandheelkundige zorg hebben subperiostale implantaten effectiever en veiliger gemaakt. Deze evolutie leidde tot het ontstaan van een nieuw "high-tech" subperiostaal implantaat, bekend als het additively manufactured subperiosteal jaw implant (AMSJI).

Om de effectiviteit van AMSJI te beoordelen, worden in hoofdstukken 2 en 3 de klinische resultaten gerapporteerd evenals de impact op de botmorfologie van de maxilla. Binnen de beperkingen van de korte follow-up vertoonde AMSJI veelbelovende resultaten als behandelingsoptie voor patiënten met ernstige kaakatrofie. De hoge verwachtingen van de patiënten werden zonder complicaties waargemaakt.

In hoofdstuk 4 wordt de patiënten tevredenheid en klinische uitkomsten gerapporteerd bij veertig patiënten met een gemiddelde follow-up tijd van 917 dagen. De gemiddelde score van de Oral Health Impact Profile (OHIP-14) was 4.20, wat wijst op een positieve invloed op de mondgezondheid. De gemiddelde algehele tevredenheidsscore op de Numerieke Rating Schaal (NRS) was 52.25. Prothetische rehabilitatie werd succesvol bereikt bij alle patiënten. De hoge tevredenheidsscores van de patiënten benadrukken de effectiviteit van AMSJI.

In hoofdstuk 5 wordt de respons van de zachte omringende weefsels op AMSJI in de maxilla bekeken. Risicofactoren voor recessie worden besproken en geïdentificeerd. Na het uitvoeren van een grondige analyse werd een dun biotype en de aanwezigheid van mucositis gecorreleerd met recessie van de omliggende mucosa.

Hoofdstukken 6 en 7 hebben tot doel inzicht te verkrijgen in de verschillende oppervlaktebehandelingen van een titaniumlegering en hun effect op de omliggende (niet-) gekeratiniseerde mucosa. Biomolecuulcoatings, met name fibroblastgroeifactor-2 en een biomimetische apatietcoating, lieten veelbelovende resultaten zien. Sharpey-like vezels die bijna loodrecht op het implantaatoppervlak aanhechten, werden aangetoond. Dit duidt op een bijna natuurlijke connectie van het implantaat en het omliggende zachte weefsel.

In hoofdstuk 8 wordt een grondige analyse en interpretatie van de onderzoeksresultaten gegeven. We gaan in op de klinische implicaties, resultaten en beperkingen van de verschillende geïncludeerde studies. Tevens worden de bevindingen en resultaten vergeleken met eerdere studies in het vakgebied. Bovendien doen we op basis van de inzichten die we hebben opgedaan in dit proefschrift, een voorstel om specifieke gebieden voor toekomstig onderzoek aan te pakken, gericht om de levensduur en effectiviteit van subperiostale implantaten nog te verbeteren.

Summary

Masticatory rehabilitation of the severely atrophied maxillae (Cawood V-VIII) has always presented a significant challenge for clinicians alike. Different preprosthetic surgical techniques are employed to enhance the retention of traditional removable dentures. However, these methods face limitations and can be associated with a significant patient morbidity.

Dahl first introduced the subperiosteal implant in the 1940s and although long-term survival of classic subperiosteal implants has been documented, they experienced numerous failures for various reasons. Subperiosteal implants, are now experiencing a resurgence in popularity. Advances in technology and materials, the rise of modern dentistry and the public's attention to oral hygiene have made subperiosteal implants more effective and safer. This evolution has given rise to a new "high-tech" subperiosteal implant known as the additively manufactured subperiosteal jaw implant (AMSJI).

To assess the efficacy of AMSJI, in Chapters 2 and 3, patient and clinician-reported outcomes, as well as the impact on maxillary bone morphology, were studied in fifteen consecutive patients with a one-year follow-up period. AMSJI demonstrated promising results as a treatment option for patients with severe upper jaw atrophy. The high patient expectations were met without complications.

Chapter 4 delved into patient-reported satisfaction and clinical outcomes in forty patients with an average follow-up time of 917 days. The mean Oral Health Impact Profile (OHIP-14) score was 4.20, indicating a positive impact on oral health, and the mean overall satisfaction rating on the Numeric Rating Scale (NRS) was 52.25. Prosthetic rehabilitation was successfully achieved for all patients, highlighting the value of AMSJI as a treatment option for individuals with severe upper jaw atrophy. The high patient satisfaction rates further underscore its effectiveness.

In Chapter 5, the focus shifted towards understanding the soft tissue response to AMSJI in the maxilla and identifying risk factors for soft tissue recession. Several risk drivers were evaluated, and it was observed that the collapse of soft tissues

around the AMSJI, leading to exposure of the framework arms, correlated with a thin biotype and the presence of mucositis.

Chapters 6 and 7 aimed to gain more insights into the different types of surface treatments of titanium implants and the effect on the interface between the implant and (non)keratinized tissue. Biomolecule coatings, particularly fibroblast growth factor-2 entrapped in a biomimetic apatite coating, showed promise in promoting a natural soft tissue attachment with Sharpey-like fibers attaching almost perpendicular to the implant surface.

In Chapter 8, we provide a comprehensive analysis and evaluation of the findings mentioned in this dissertation. Our analysis contrasts these findings with related studies within the same field of study and focuses on the implications, limitations, and significance of these results. After learning more from this research study, we also suggest particular domains for extensive future exploration that can significantly improve subperiosteal implants.

Table of content

Chapter I: Introduction

Background: edentulism “final marker of disease burden for oral health”

Oral health is crucial for overall well-being, as it has a profound impact on quality of life, self-esteem, and physical health[1]. However, oral health problems can be a significant burden, causing discomfort, pain, and impaired function. Among the most severe oral health problems is edentulism, which has been a major problem since the dawn of time and is frequently described as the “final marker of disease burden for oral health”[2].

Edentulism is the loss of teeth in either the maxilla and/or mandible. Depending on the number of teeth lost, edentulism can be classified as either partial or complete. Mostly the reasons for developing edentulism are multifactorial[3]. However, poor oral hygiene is a major risk driver for edentulism, as it can lead to periodontal disease, tooth decay and subsequently loss of teeth. Lifestyle factors, such as smoking, alcohol consumption, and poor diet, can also contribute to edentulism, increasing the risk of oral health problems. Age is another significant risk factor for edentulism, as tooth loss is more common in older individuals[3-4].

Although the prevalence of edentulism declined over the last decades, it is still considered a major issue worldwide[3-4]. Dentition is necessary for proper mastication, and the loss of teeth can significantly affect an individual's ability to chew, swallow, and speak. This can lead to difficulties in eating and digestion, inadequate nutrient absorption, and malnutrition. Additionally, edentulism can alter the microbial content of the oral cavity, increasing the risk of oral infection and periodontal disease. This may result in a variety of unfavorable effects, including pain, inflammation, and bone resorption, as well as structural health issues like diabetes, cognitive impairment, or cardiovascular disease. Patients can also suffer from significant psychological impacts as tooth loss can cause anxiety, depression, and social isolation[5].

Overall, edentulism is a significant public health issue that can have wide-ranging impacts on individuals, healthcare systems, and society[2,5].

Oral rehabilitation of the atrophic maxilla: current methods and pitfalls

In general, (complete) edentulous patients are left with two options when oral rehabilitation is desired. One of the options is a removable denture to restore the loss of teeth. This type of denture relies on the underlying soft tissues and remaining bone for support, retention, and stability. However, one of the associated problems of edentulism is the significant effect on the alveolar ridge[2]. Patients who remain edentulous for a long time may suffer from disuse atrophy resulting in a vestigial alveolar crest[4-5]. The continuous resorption may lead to a reduced denture-bearing area, making retention and stability of a removable prosthesis challenging or sometimes even impossible. These patients are left with ill-fitting dentures and the associated problems in mastication, speech and functional and sensory deficiencies in the oral mucosa, salivary gland and musculature[5]. Denture adhesives or relining sessions are frequently advised as a last resort to improve retention and stability of their prosthesis.

When an edentulous patient wishes a fixed option, an implant-supported denture is advised. This type of denture does not rely on the surrounding tissue for support but rather on endosseous implants placed in the alveolar processus. However, when advanced resorption of the jawbone occurs, insufficient bone width and/or height may make placement of endosseous implants impossible. The use of short, narrow, or tilted implants has been opted to circumvent this problem. However, a minimum level of bone volume is still needed, so patients suffering from extremely atrophied jaws are not eligible for placement of these implants. See figure 1.

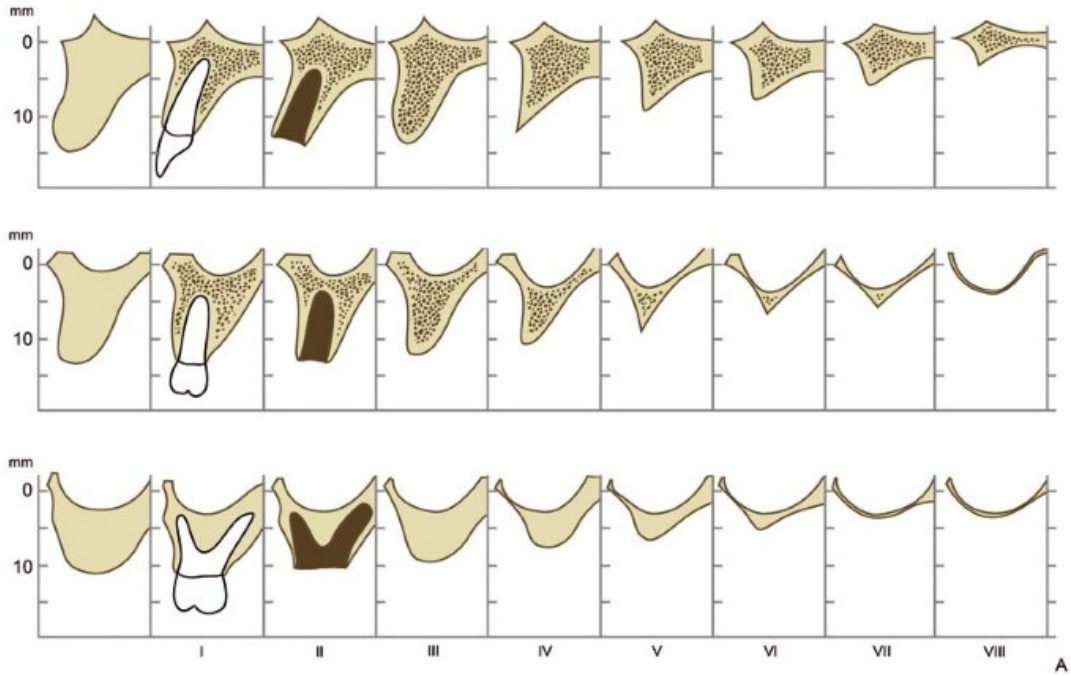

Figure 1. The Cawood and Howell classification categorizes edentulous maxillae into eight classes based on the extent of bone resorption. Ranging from minimal (Class I) to complete loss of bone (Class VIII). Classes guide clinicians in selecting appropriate interventions, from conventional dentures to advanced prosthetic designs or reconstructive surgery, depending on the severity of bone atrophy.

When a patient has an extremely atrophic maxilla, only few treatment options exist:

1. Augmentation of the alveolar crest using bone grafts:

Bone grafting is a surgical procedure that involves transplanting bone tissue to increase the width and height of the atrophic area to provide a solid foundation for placement of endosseous implants. See figure 2. Different types of bone grafts are used in clinical practice and can be classified as autogenous, alloplastic, xenogenic, and allogenic[6]. Autogenous bone is regarded as the golden standard due of its biocompatibility, osteoinductive, osteoconductive and osteogenic properties[6].

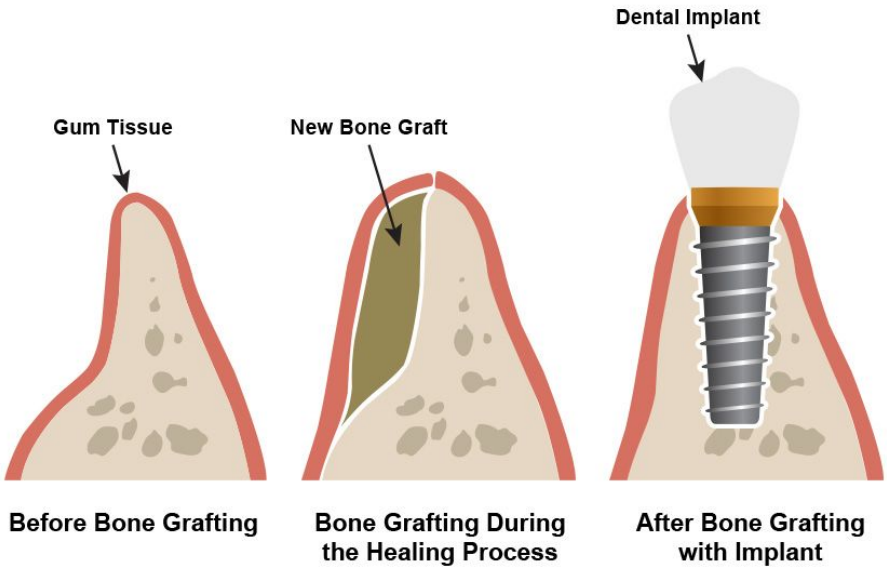

Figure 2. Schematic overview of the effect of bone grafting

Autogenous bone grafts can be harvested from intraoral and extraoral donor sites. Intraoral autogenous osseous grafts include the mandibular symphysis, mandibular ramus, angle of the mandible, maxillary tuberosity, and intraoral exostoses. Several autogenous bone grafting techniques, such as guided bone regeneration, inlay grafting and autogenous onlay block grafting can be used to increase the available bone volume needed for implant placement[7]. However, the amount of bone that can be harvested from intraoral donor sites is limited and in patients where significant bone volume is already lost, the intraoral donor sites may not provide sufficient graft material.

When an extraoral donor site for bone harvesting is needed, both the iliac crest and calvarium serve as valuable options for providing the necessary bone material to enlarge an alveolar crest, depending on the specific needs and characteristics of each patient's case. The iliac crest is a frequently used donor site due to its large availability of cancellous bone. It provides a reliable source of bone grafts for augmentation procedures in the alveolar ridge. On the other hand, the tabula externa of calvarian bone offers the opportunity to obtain larger amounts of cortical bone for more extensive augmentations.

However, there are certain drawbacks of using autologous bonegrafts and success of the procedure depends on several factors. Bone grafting and bone regeneration relies

on the individual osteogenic property, which varies strongly among patients and diminishes with age[7]. As a result, an unpredictable degree of resorption is seen. Furthermore, substantial resorption occurs which influences functional stability and esthetics of the endosseous implants. If the graft undergoes further resorption there may be a necessity to repeat the bone augmentation to ensure proper volume for re-implantation. Furthermore, it is important to note that the procedure carries relevant morbidity associated with the harvesting and installation of bone grafts at both the recipient and donor sites. The risk of bleeding, dehiscence, pain, infection, swelling, neurosensory deficits and graft failure remain imminent. Another major disadvantage is that the harvested bone blocks are of finite thickness and only a limited volume of bone can be restored, rendering complete augmentation of a severely atrophied maxilla difficult. Also, a waiting period after bone grafting for implantation of 4–6 months is needed to ensure bone integration and remodelling.

2. Zygomatic implants

Zygomatic implants may be used as an alternative to bone grafts for rehabilitation of the edentulous atrophic upper jaw. These implants are anchored in the zygomatic bone, which is more dens and stronger than the maxilla. See figure 3. Also, the know disuse atrophy as seen at the alveolar process, is not present. Zygomatic implants provide a secure and durable solution for individuals with severe bone loss in the upper jaw. They allow patients to regain functional and aesthetic benefits by supporting dental restorations, improving chewing ability, speech, and overall oral quality of life[8-9].

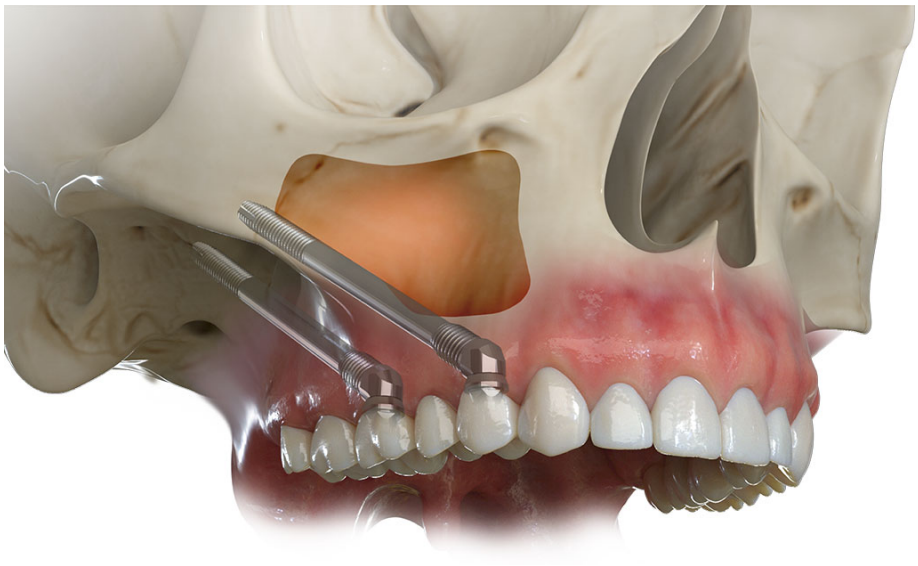

Figure 3. Zygomatic implants are secured in the zygomatic bone (cheek bone) when there is insufficient quality or quantity of maxillary bone for classic endosseous implants

Zygomatic implants have proven their value in the past and some studies demonstrated a higher predictability compared to alveolar crest augmentation techniques using autologous bone[8]. However, the success rate has been less extensively described, often relying on scientific evidence rather than the patient's perspective. Quality-of-life studies have rarely addressed maxillary atrophy grades, usually only referring to "severe" and "major" atrophy as justification for zygomatic implant placement[8-9].

The use of zygomatic implants for severely resorbed maxillae is an option, but like any surgical procedure, placing zygomatic implants carries inherent risks and complications. Many of these complications overlap with those associated with classic endosseous implant placement, including bleeding, swelling, infection, and failure of osseointegration. Additional complications specifically associated with zygomatic implants may include sinusitis, oroantral fistula formation, periorbital and conjunctival hematoma or edema, epistaxis and generalized facial pain[10]. More serious complications can involve infraorbital nerve paresthesia due to the implant's proximity, orbital floor perforation with consequent diplopia (and even blindness), and infratemporal fossa perforation[10-11].

When complications arise, the removal of zygomatic implants can be challenging and frequently results in substantial bone loss, which can worsen the patient's health due to the already limited bone volume in the maxilla. Therefore, zygomatic implant placement should always be considered as a major surgical procedure that requires the expertise of skilled and experienced clinicians.

3. Other alternative solutions

The “All-on-4“ principle was developed to maximize the use of available remnant bone in atrophic jaws and uses only four dental implants to provide edentulous patients with an immediately loaded full arch restoration[12]. See figure 3. However, this procedure is highly technique-sensitive, necessitating meticulous pre-surgical preparation involving tools such as CAD/CAM and surgical splints. Furthermore, this method is not applicable to all edentulous patients, as a prerequisite for successful endosseous implant placement is enough bone, a condition challenging to meet in a fully atrophic maxilla. If any issues arise or changes are required, significant alterations to the existing structure or even complete replacement of the restoration may be necessary[13]. Another disadvantage is the risk of implant failure associated with fewer implants supporting the prosthetic restoration. The concentration of load distribution on a smaller number of implants increases the stress, potentially leading to a higher risk of failure, especially if proper oral hygiene is not maintained or if excessive force or pressure is exerted on the restoration[13].

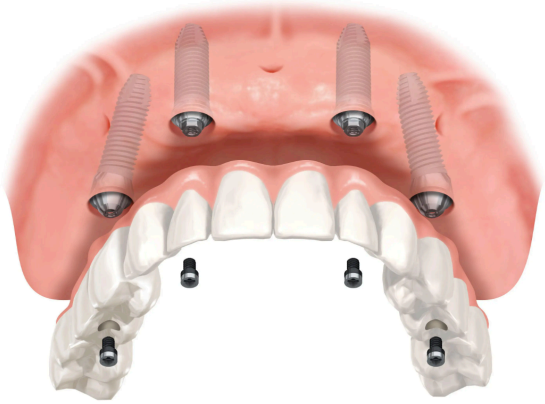

Figure 3. The "All-on-4" technique involves the strategic placement of four endosseous implants to support a complete denture, providing stability and functionality

Pterygoid implants are another option for oral rehabilitation of the atrophic maxilla. These implants are anchored between both the wings of pterygoid process of sphenoid bone[14]. See figure 4. However, for full arch rehabilitation, only pterygoid implant use is not advisable as placement of two conventional implants in the anterior region is necessary for adequate support[14-15]. Furthermore, pterygoid implants are not suitable for all patients, as the anatomy of the posterior maxilla must meet specific criteria, including adequate bone density and quality, for successful placement[15]. The intricate nature of pterygoid implant surgery also heightens the risk of complications compared to conventional implant procedures. Possible complications include injury to adjacent structures such as the pterygoid vascular plexus and sinus perforation[15].

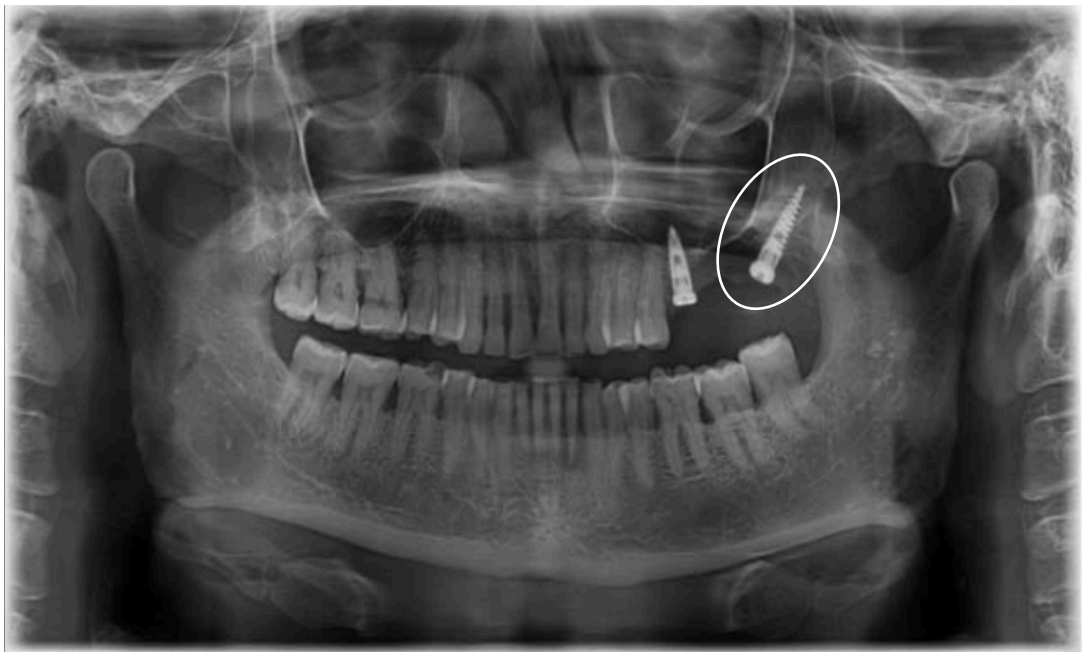

Figure 4. Pterygoid implants (white circle) are a specialized type of dental implant placed in the pterygoid plate, addressing severe bone loss in the posterior maxilla. These implants offer an alternative when traditional implants are not feasible due to inadequate bone.

The flapless placement of mini dental implants may serve as another alternative. These mini-implants have a smaller diameter when compared to traditional dental implants and typically range from 1.8 mm to 3.3 mm. See figure 5. However, flapless mini-implants do not offer the same level of stability and load-bearing capacity as standard-sized dental implants as the primary load-bearing area for these implants is in the cortical bone. Favourable outcomes are described in specific applications, although several publications have reported high failure rates[17-19]. Therefore, this treatment is aimed particularly at medically and financially compromised patients[18-19].

Figure 5.
Left: a "traditional" endosseous implant
Right: a mini implant

Subperiosteal implants, what was old becomes new

Subperiosteal implants were first introduced in the 1940s and have been used for decades in the field of oral rehabilitation[20]. This type of dental implant is placed beneath the periosteum and designed to sit directly on the alveolar crest. Connection of the implant to the prosthesis is made using four to six per-mucosal extensions, fixating the implant to the prosthesis.

Subperiosteal implants have distinct advantages. They are particularly suitable for patients with insufficient bone quality or quantity, such as severe bone atrophy or poor bone density. Unlike endosseous implants, subperiosteal implants are placed beneath the periosteum and fit onto the alveolar process, eliminating the need for bone grafting procedures. This simplifies the surgery and reduces treatment time. Additionally, subperiosteal implants may allow for immediate or early loading, enabling quicker functional and aesthetic improvements compared to delayed loading protocols.

Their popularity waned due to the rise of endosseous screw-type implants, which are much more commonly used today[20]. The decline in subperiosteal implants resulted from several factors[21]. Firstly, endosseous titanium implants proved to be more effective and had a higher success rate compared to chrome-cobalt-molybdenum subperiosteal implants. Titanium endosseous implants are directly placed in the jawbone, leading to stronger fusion with the bone through osseointegration. Secondly, complications such as early and late implant exposure, severe bone resorption, and fistulation were reported with subperiosteal implants, causing increased implant mobility, discomfort, and failure. The metal framework used in subperiosteal implants was susceptible to hypersensitivity type IV, corrosion and breakdown, which could harm surrounding bone and soft tissue. Furthermore, the surgical procedure for subperiosteal implants was more invasive, requiring longer healing time compared to endosseous implants. Additionally, subperiosteal implant fabrication techniques were complex and caused considerable patient discomfort during preparation.

Additively Manufactured Subperiosteal Jaw Implants (AMSJI)

The Additively Manufactured Sub-Periosteal Jaw Implant (AMSJI) was conceptualized as a viable alternative to zygoma implants and the extensive bone grafting procedures required for individuals with Cawood and Howell Class V–VIII bone atrophy. The fabrication process of the AMSJI involves a dual scanning methodology. Initially, a multi-slice or cone beam computed tomography (CBCT) of the maxillofacial complex is conducted with a scanning prosthesis in centric occlusion. Additionally, a high-resolution scan, whether optical or X-ray, exclusively captures the scan prosthesis to aid in the implant design and generate a language file (STL) (Materialise Medical 24.0; Materialise, Leuven, Belgium). Utilizing these imaging data, the AMSJI is formulated as two distinct subunits. Each AMSJI comprises two wings strategically positioned on the midfacial pillars (canine and zygomatic buttresses), regions resistant to disuse atrophy and generally possessing adequate thickness for achieving primary stability through osteosynthesis screws. These areas correspond to those employed for plate osteosynthesis in Le Fort I-type repositioning procedures. The wings are linked to a basal loop-shaped frame, and three arms connect to three transmucosal posts, which, in turn, attach to the preliminary 3D-printed prosthesis crafted from NextDent polymer (Soesterberg, the Netherlands). Both sub-periosteal implants are additively manufactured using titanium grade 23 ELI (extra-low-Interstitials) by CADskills BV, Ghent, Belgium. A definitive hybrid bridge or final primary matrix-patrix structure is affixed to the transmucosal posts starting from three months postoperatively. See figure 6 and 7.

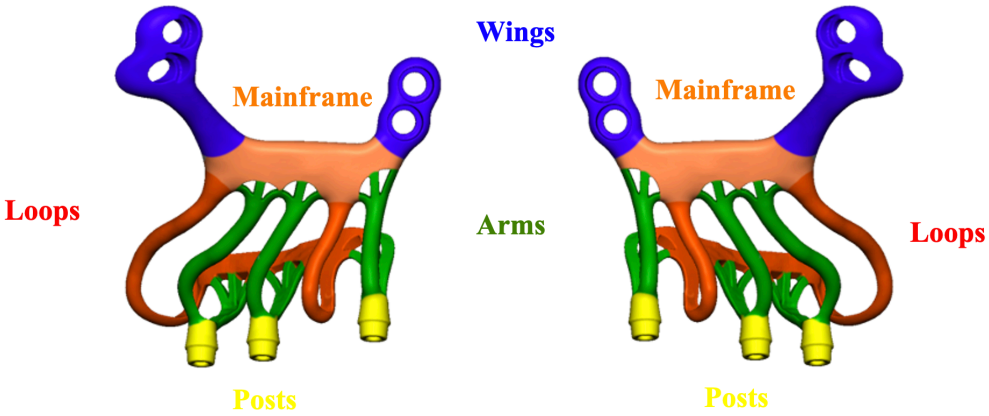

Figure 6. Colour-coded components of both AMSJI subunits

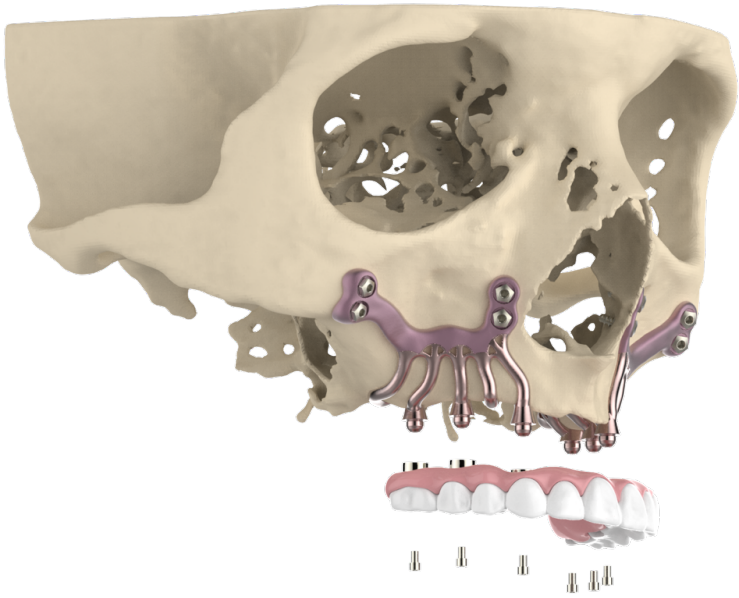

Figure 7. Computer image of both AMSJI subunits fixed with osteosynthesis screws on the canine and zygomatic buttresses. A temporary prosthesis is attached to both subunits via the transmucosal posts

Aim of the study

Subperiosteal implants are experiencing a resurgence in popularity. Advances in technology and materials, the rise of modern dentistry and the public's attention to oral hygiene have made subperiosteal implants more effective and safer and allowed for a revisitation of this old technique.

The objective of this thesis was to evaluate the clinical outcomes in edentulous patients with a Cawood–Howell atrophy classification ≥ V after maxillary rehabilitation with a novel sub-periosteal jaw implant: the AMSJI (additively manufactured subperiosteal jaw implant). Furthermore, a comprehensive review of the literature is conducted to recommend surface modifications that can enhance the biofunctional attributes of this 3D-printed subperiosteal titanium implant. Various methods aimed at optimizing the implant's surface properties, with the goal of enhancing biocompatibility, are explored and critically investigated.

Efficacy needed to be proven in long-term observational studies. In Chapter 2 and 3, we studied patient-and clinician-reported outcomes together with the effect on maxillary bone morphology after rehabilitation of the atrophic maxilla with AMSJI in fifteen consecutive patients with a follow up period of 1 year.

Chapter 4 further investigates patient-reported satisfaction and clinical outcomes in forty patients with a mean follow up time of 917 days after AMSJI installation.

In chapter 5 we aim to describe the soft tissue (keratinized and nonkeratinized mucosa) response to AMSJI in the maxilla and to identify risk factors for soft tissue recession.

In chapter 6 and 7, we focus on gaining more insight into the effect of surface treatment of titanium (Ti) implants on the Ti implant-(non)keratinized tissue interface.

Chapter 8 offers a detailed examination and understanding of our research findings, encompassing a thorough analysis and interpretation. We extensively explore the implications, limitations, and significance of the outcomes, drawing comparisons with existing studies in the field. Moreover, building upon the knowledge acquired during this PhD, we put forward suggestions for future research to augment the effectiveness of subperiosteal implants with the goal to elevate the overall quality, success rates, and patient outcomes.

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Chapter II: Patient- and clinician-reported outcomes for the additively manufactured sub-periosteal jaw implant (AMSJI) in the maxilla: prospective multicentre one-year follow-up study

Van den Borre C, Rinaldi M, De Neef B, Loomans NAJ, Nout E, Van Doorne L, Naert I, Politis C, Schouten H, Klomp G, Beckers L, Freilich MM, Mommaerts MY. Patient- and clinician-reported outcomes for the additively manufactured sub-periosteal jaw implant (AMSJI) in the maxilla: a prospective multicentre one-year follow-up study. Int J Oral Maxillofac Surg. 2022 Feb;51(2):243-250. doi: 10.1016/j.ijom.2021.05.015.

Abstract

The clinical outcomes of maxillary rehabilitation with the additively manufactured sub-periosteal jaw implant (AMSJI; CADskills BV, Ghent, Belgium) were evaluated in edentulous patients with a Cawood–Howell atrophy classification ≥ 5 in all regions of the maxilla. Fifteen consecutive patients were included in the study and were followed up for 1 year. They were interviewed using a survey protocol and were examined clinically and radiographically preoperatively (T0) and at 1 (T1), 6 (T2), and 12 (T3) months after permanent upper prosthesis placement. The overall Oral Health Impact Profile-14 score at T0 was a mean 17.20 (standard deviation 6.42). At T3 a mean value of 5.80 was seen (standard deviation 4.18). When comparing T0 to T3, results were also significant (*P*-value 0.001). General satisfaction based on the numerical rating scale was a mean 49.93 at T1, which was less than patient expectation prior to treatment at T0 (52.13). A higher overall value was seen at T3 (53.20) when compared to T0. Within the constraints of the short follow-up, the AMSJI appears to be a promising tool for patients with extreme jaw atrophy. The high expectations of patients were met without complications.

Keywords: maxilla, edentulous jaw, sub-periosteal implantation, alveolar bone loss, patient satisfaction

Introduction

An implant-retained prosthesis is a commonly used treatment option in the rehabilitation of edentulous patients[1]. Advanced resorption of the jawbone may occur, particularly in the maxilla, resulting in insufficient bone width and/or height to allow the placement of endosseous implants. These patients have traditionally very few rehabilitation options, each associated with risks[2,3]. The additively manufactured sub-periosteal jaw implant (AMSJI; CADskills BV, Ghent, Belgium) is a contemporary new alternative[4] (Fig. 1). The AMSJI revisits the almost 80-year-old concept of sub-periosteal implants and uses the midfacial pillars for fixation with osteosynthesis screws. These pillars do not undergo marked atrophy, and their sufficient thickness ensures primary stability to support the 3D printed titanium structure. With the earlier proof-of-concept of the AMSJI[5], this made-to-measure option provides immediate functional restoration within one intervention.

The efficacy of the AMSJI needs to be proven in long-term prospective registries or observational studies. The aim of this study was to evaluate the clinical efficacy of the maxillary AMSJI treatment protocol after 1 year.

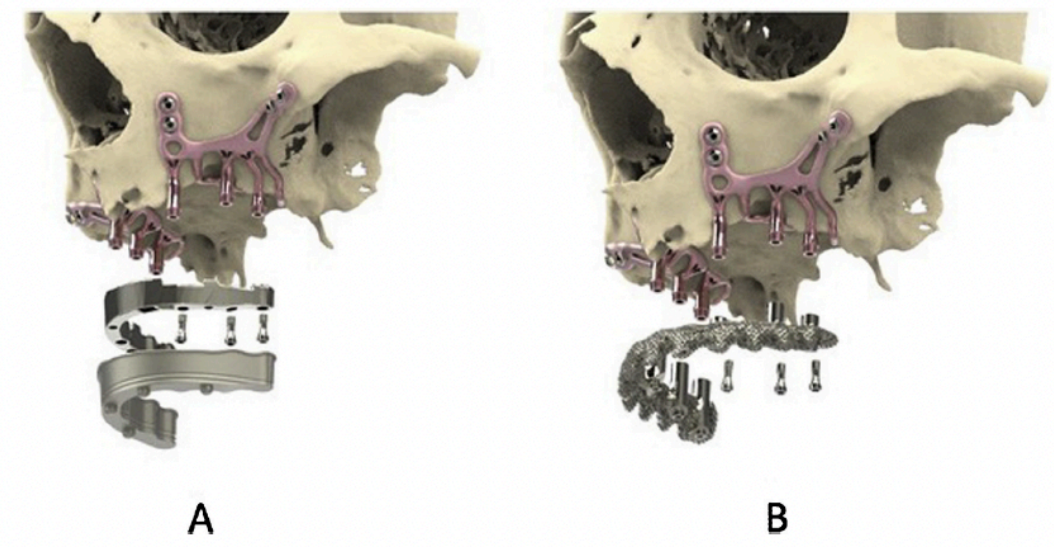

Fig. 1. The AMSJI with double structure (A) and hybrid bridge (B) suprastructure option

Patients and methods

A multicentre study was conducted by the International Workgroup on AMSJI. Fifteen Belgian, Dutch, and Italian patients participated and were followed up for 1 year after instalment of the permanent restoration. The inclusion criteria were as follows: all consecutive patients who underwent bilateral AMSJI placement in the maxilla and who themselves and their surgeon agreed to collaborate in the study before their inclusion. Placement of the AMSJI was performed under local or general anaesthesia based on the technique described by Mommaerts in 2017[4]. After the surgery, a temporary additively manufactured NextDent prosthesis was positioned in proper occlusion with the lower dental arch. The definitive restoration was constructed 2 months later[4].

Data collection

Evaluations were performed preoperatively (T0), and at 1 (T1), 6 (T2), and 12 (T3) months after prosthesis installation. All the surveys were anonymized using a patient code. The survey comprised three sections. The first section collected general information including the Cawood–Howell grade of atrophy, details of comorbidities, the time of implantation, and general information concerning the surgery. The second section collected objective data (clinical and radiological) and was completed by the surgeon at fixed intervals. At T0, a check was performed for sinusitis according to the Lanza–Kennedy staging[6] and radiological sinusitis according to the Lund–Mackay computed tomography (CT) staging[7]. The degree of comfort experienced by the patient with their prosthesis (discomfort, speech, and hindrance in maintaining good oral hygiene) was recorded as well. The stability of the AMSJI after unmounting the prosthesis (overdenture with connecting bar or hybrid fixed full prosthesis) from both the left and right AMSJIs was also evaluated (T1, T2, and T3). The health of the keratinized mucosa around the different posts of the AMSJI was also studied over time. Fig. 1 gives more information concerning the locations of the posts. Complications such as infection, pain, fracture of a post, or the need for urgent removal of any AMSJI or post were recorded as well. The third section collected subjective data in the form of patient-reported outcome measures (PROMs). These were also collected at T0, T1, T2, and T3. Patients were interviewed using the short form of the Oral

Health Impact Profile-14 (OHIP-14)[8], which comprises 14 questions covering functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicaps. Patient satisfaction was also assessed using numerical rating scales (NRS)[9]; six questions were asked, covering aesthetic benefit, chewing, comfort, phonetics, cleaning, and general satisfaction. At T0, the patient's expectation of the treatment outcome was tested. The result was than compared after AMSJI installation at T1-T2 and T3.

Interpretation of the objective data

Most of the objective data (see section 2) were collected using a dichotomous table with assigned values of 0 or 1, with 1 being the total score and representing the presence of any sinusitis (radiological and/or clinical) or mobility. The mobility of each AMSJI was tested manually by the clinician after unscrewing the final restoration. The condition of the tissue around the posts (peri-post tissue condition) was the only exception. This was graded using a four-point scale ranging from 0 to 3: 0, no inflammation; 1, slight colour change and oedema; 2, redness/glazing; 3, marked redness/inflammation/ulceration.

Interpretation of the subjective data

Each question of the OHIP-14 was scored using a five-point scale: 0, never; 1, hardly ever; 2, occasionally; 3, fairly often; 4, very often or every day. The domain scores of the OHIP-14 were obtained by summing the responses to the two corresponding questions, and overall scores were derived by summing the seven domain scores. In total, the score could range from 0 to 56 with domain scores ranging from 0 to 8[8]. The higher the OHIP-14 score, the poorer the oral health-related quality of life (OHRQoL). The NRS is based on the visual analogue scale (VAS) and aims to quantify characteristics that cannot easily be measured directly. The present study included six questions answered with a NRS on an 11-point scale ranging from '0' representing 'not satisfied at all' to '10' representing 'very satisfied'. A total score was calculated by summing the responses. The total score value could range between 0 and 60, with 60 being the highest possible satisfaction and 0 the very worst.

Statistical analysis

The data were analysed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) for macOS Mojave. The mean and standard deviation (SD) values were calculated for the OHIP-14 scores. The OHIP-14 scores (overall and domain level) of adjacent stages were compared using the Wilcoxon signed-rank test: T0 compared with T1, T1 compared with T2, T2 compared with T3, and T3 compared with T0 to determine critical time intervals. The NRS scores (overall and for each question) were also compared between the time points using the Wilcoxon signed-rank test.

Results

Eight male patients (mean age 57.38 years, SD 8.70 years) and seven female patients (mean age 62.17 years, SD 3.43 years) were followed up for 1 year after receiving their final prosthesis. In total, 60 surveys were completed and analysed.

Stability of the AMSJI subunits

No mobility of the left or right AMSJI was observed at any time point. The results are presented in Table 1.

Table 1. Stability of the AMSJI subunits.

Time point	No mobility, *n*	Mobility (>0 mm), *n*
T1	30	0
T2	30	0
T3	30	0

Mobility reported per unilateral AMSJI (n = 30). T1, 1 month after prosthesis installation; T2, 6 months after prosthesis installation; T3, 12 months after prosthesis installation.

Rhinosinusitis

Four patients reported clinical rhinosinusitis according to the Lanza and Kennedy staging[6] at T0 and at T1. However, no aggravation of the clinical symptoms was reported at T2 or T3. Five patients were found to have radiological rhinosinusitis according to the Lund–Mackay CT staging[7] at T0. Four of them were also diagnosed with clinical rhinosinusitis. Both clinical and radiological rhinosinusitis appeared to disappear over time, with one patient reporting sinusitis at T2 and no patients reporting problems at T3. The results are presented in Table 2.

Table 2. Clinical and radiological rhinosinusitis.

Time point	Clinical rhinosinusitis		Radiological rhinosinusitis	
	Present	Not present	Present	Not present
T0	4	11	5	10
T1	4	11	4	11
T2	1	14	1	14
T3	0	15	0	15

The presence and/or absence of rhinosinusitis (clinical and radiological) at the different time points. T0, preoperatively; T1, 1 month after prosthesis installation; T2, 6 months after prosthesis installation; T3, 12 months after prosthesis installation

Reported complication(s)

No complications were reported at any time point, and no post had to be removed because of inflammation, infection, or fracture.

Peri-post tissue condition

The peri-post tissue condition was measured and analysed based on the four-point scale described above. Mean values were calculated for each post at each time point and these are presented in Table 3. Generally, colour changes and oedema were observed at T1, with reported mean values ranging between 0.00 and 0.53. Posts 3 and 4 were more prone to inflammation at T1, T2, and T3 (Fig. 2).

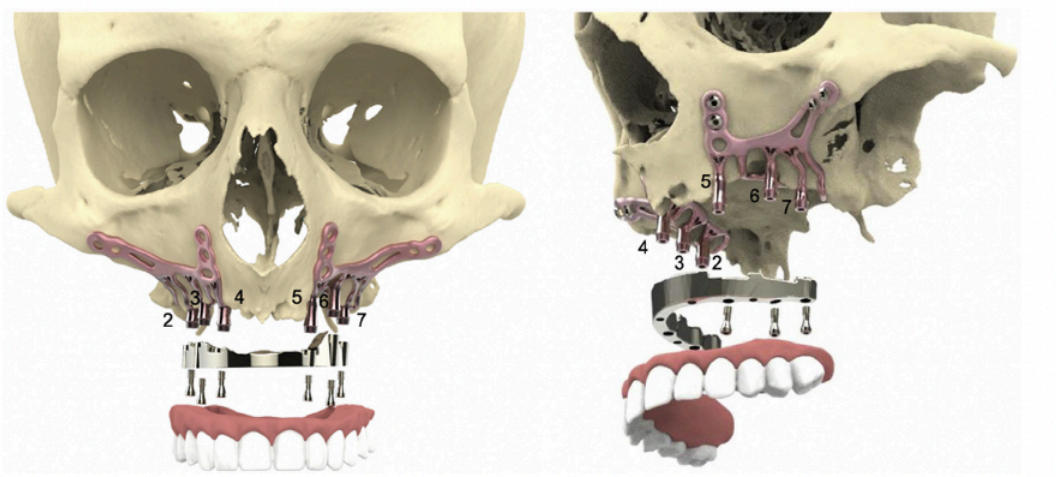

Fig. 2. Left and right AMSJI in frontal and side views, with the numbered posts, the connecting bar structure, and the overdenture

Table 3. Peri-post tissue condition at each time point: mean scores on a four-point scale.

Post of the AMSJI	T1	T2	T3
1	/	/	/
2	0.40	0.40	0.13
3	0.53	0.53	0.40
4	0.67	0.47	0.27
5	0.33	0.27	0.13
6	0.27	0.27	0.13
7	0.33	0.13	0.07
8	/	/	/

The mean values of the peri-post tissue condition were calculated for each post at each time point. At T1, posts 2 to 7 all showed minor inflammation. This improved, but some redness was still seen at T3 around posts 3 and 4. All patients had an AMSJI designed with 6 posts (post 2 – 7). For this reason, no value could be calculated for post 1 and 8.

Oral Health Impact Profile-14 results

The overall OHIP-14 score was calculated to provide a general representation at the set time points. A mean value of 17.20 (SD 6.42) was calculated at T0, 8.93 (SD 5.30) at T1, 7.80 (SD 4.96) at T2, and 5.80 (SD 4.18) at T3 (Tables 4 and 5). The *P*-values for the comparisons of OHIP-14 values between the different time points are reported in Table 4. At each successive postoperative time point, the mean score rating decreased, indicating a higher OHRQoL. Each domain was also evaluated separately (Tables 4 and 5). The mean overall OHIP-14 score for all patients at each time point is visually represented in Fig. 3.

Table 4. Results of the Oral Health Impact Profile-14 (OHIP-14) at the different time points.

	T0		T1		T2		T3	
Domain	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Overall OHIP-14	17.20	6.42	8.93	5.30	7.80	4.96	5.80	4.18
1. Functional limitation	2.80	1.52	2.00	1.36	1.53	1.19	1.20	1.08
2. Physical pain	3.27	1.52	2.07	1.44	1.53	1.19	1.20	1.01
3. Psychological discomfort	1.73	2.19	0.93	1.22	1.13	1.25	0.73	1.10
4. Physical discomfort	3.33	2.16	1.80	1.66	1.47	1.51	1.07	0.96
5. Psychological disability	2.53	1.96	1.00	1.07	1.00	0.85	0.73	0.80
6. Social disability	2.20	1.90	0.47	0.92	0.47	0.83	0.53	0.92
7. Handicap	1.33	1.63	0.67	0.98	0.67	0.98	0.33	0.72

SD, standard deviation. The table reports the overall general values of the OHIP-14 and the values for each domain. At T0, OHIP-14 values were high, with a mean value of 17.20. This value decreased over time, with a mean value of 5.80 at T3, meaning a very high level of satisfaction.

Table 5. Significance of differences in Oral Health Impact Profile-14 (OHIP-14) values between the different time points.

	T0 to T1	T1 to T2	T2 to T3	T0 to T3
Domain	*P*-value	*P*-value	*P*-value	*P*-value
Overall OHIP-14	0.001*	0.117	0.005*	0.001*
1. Functional limitation	0.290	0.121	0.260	0.018*
2. Physical pain	0.044*	0.023*	0.096	0.002*
3. Psychological discomfort	0.084	0.257	0.034*	0.071
4. Physical discomfort	0.004*	0.160	0.161	0.002*
5. Psychological disability	0.017*	1.000	0.157	0.004*
6. Social disability	0.005*	1.000	0.705	0.007*
7. Handicap	0.015*	1.000	0.059	0.028*

Statistical analysis: Wilcoxon signed-rank test; IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) for macOS Mojave.

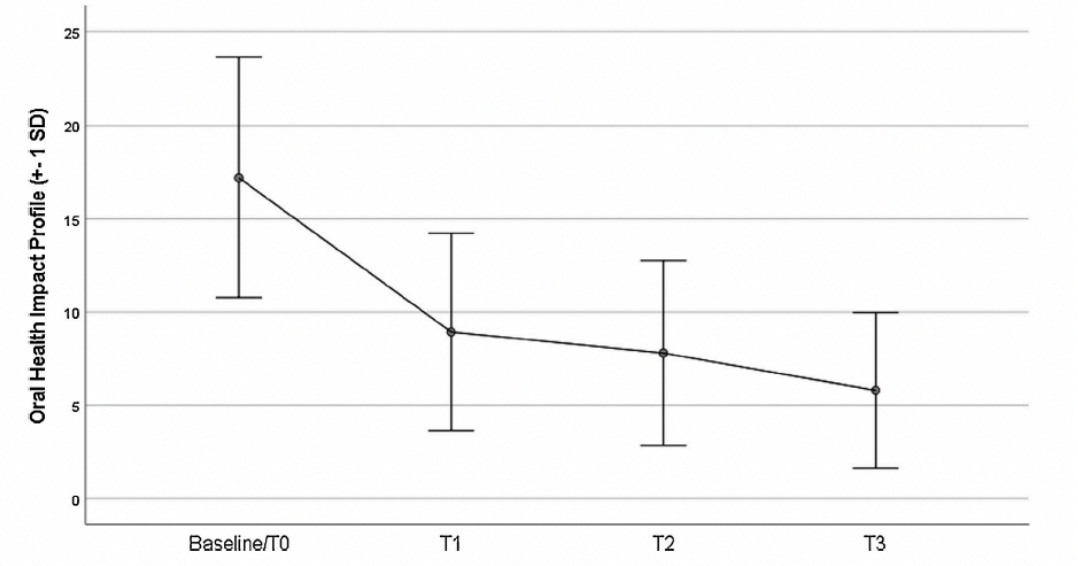

Fig. 3. Visual representation of the mean overall OHIP-14 scores for all patients at each time point.

Numerical rating scale results

The NRS questions were presented to all patients at T0, T1, T2, and T3. The patients initially reported a high expectancy of the AMSJI, with a mean score of 52.13 (SD 6.24). At T1, the mean score was 49.93 (SD 4.54). The NRS score increased to 51.20 (SD 3.80) at T2 and 53.20 (SD 3.41) at T3 (Table 6). The *P*-values for the comparisons of NRS values between the different time points are reported in Table 7. The mean overall NRS score for all patients at each time point is visually represented in Fig. 4.

Table 6. Results of the numerical rating scale (NRS) for patient satisfaction at the different time points.

	T0		T1		T2		T3	
Question	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Overall NRS	52.13	6.18	49.93	4.54	51.07	3.81	53.20	3.41
1 (aesthetic benefit)	8.67	1.11	8.27	0.96	8.53	0.74	9.00	0.65
2 (chewing)	8.60	1.18	8.00	1.36	8.53	0.64	8.93	0.88
3 (comfort)	8.60	1.18	8.60	0.91	8.87	0.64	8.67	1.45
4 (phonetics)	8.60	1.18	8.13	0.99	8.33	0.90	8.67	0.82
5 (cleaning)	8.67	1.23	8.27	1.10	8.27	1.03	8.73	0.88
6 (general satisfaction)	9.00	0.93	8.67	0.90	8.67	0.72	9.20	0.41

SD, standard deviation. The mean values for each time point are given. The mean overall NRS value decreased from T0 to T1. However, at T2 the mean value was almost the same as that at T0. T3 showed an even higher mean patient satisfaction value. Mean values are also given for each question separately.

Table 7. Significance of differences in the mean numerical rating scale (NRS) values for patient satisfaction between the different time points.

	T0 to T1	T1 to T2	T2 to T3	T0 to T3
Question	*P*-value	*P*-value	*P*-value	*P*-value
Overall NRS	0.172	0.21	0.050*	0.57
1 (aesthetic benefit)	0.163	0.21	0.008*	0.19
2 (chewing)	0.12	0.17	0.11	0.40
3 (comfort)	0.67	0.34	1.00	0.56
4 (phonetics)	0.21	0.37	0.13	0.86
5 (cleaning)	0.27	0.86	0.083	0.92
6 (general satisfaction)	0.13	1.00	0.0050*	0.44

Statistical analysis: Wilcoxon signed-rank test; IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) for macOS Mojave.

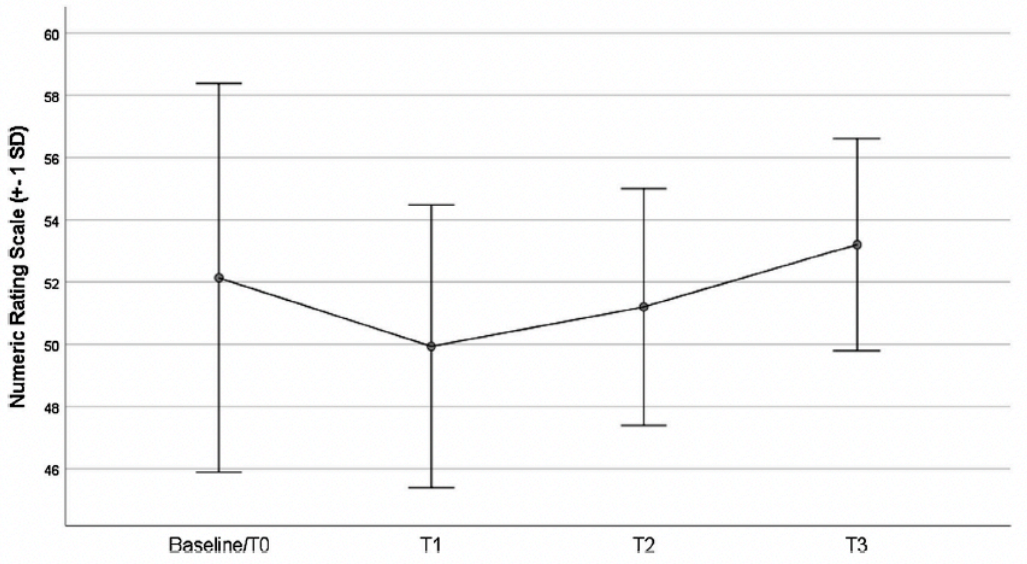

Fig. 4. Visual representation of the mean overall NRS score for all patients at each time point.

Discussion

Adequate dental articulation is crucial for good quality of life and well-being[10]. Despite many advances in preventive dentistry, edentulism remains a major public health issue worldwide. One of the main problems with losing teeth is the effect on the alveolar process. The alveolar ridge of patients who remain edentulous for a long time will become vestigial because of bone resorption[1]. Continuous resorption may result in ill-fitting dentures requiring several relining sessions and denture adhesives in an attempt to improve stability during masticatory function and speech.

Patients with extreme jaw atrophy have limited options concerning oral rehabilitation. Autogenous bone transplantation for the augmentation of the alveolar ridge remains a frequently used method. Mostly, calvarial or iliac bone is used in patients with severe to extreme atrophy[10]. Wortmann et al. (2019) evaluated patient satisfaction for both calvarial and iliac bone grafts in 20 patients with a bone height of <3 mm in the maxillary sinus area and a bone width of <2 mm in the anterior maxillary area[11]. A mean VAS score of 93 (out of 100) was achieved for all participants at 12 months after the instalment of their implant-retained maxillary overdenture. The mean OHIP-49NL was 78.80 preoperatively and decreased to 16.00 after treatment. Patient satisfaction with the AMSJI rivals the mean satisfaction value of autologous bone augmentation procedures and has the additional benefit of providing comprehensive reconstructive therapy in only one surgical intervention. Harvesting extraoral bone grafts requires an additional surgery under general anaesthesia, carrying the risk of complications and adverse effects. Although Wortmann et al. (2019) reported high satisfaction; however, several patients reported postoperative infection at the donor site, scar formation, and loss of sensitivity, and three patients reported problems with walking after 1 year. All 15 AMSJI patients in the present study remained complication free at 12 months. Furthermore, the patients did not have to undergo extra implant placement, and immediate mastication was provided.

As another alternative, the flapless placement of mini dental implants with overdenture treatment could be suggested. In cases with a high degree of resorption of the maxilla, however, not even this type of implant can be placed due to a lack of bone. Moreover, several publications have reported high failure rates, especially in the

maxilla. This treatment is therefore aimed particularly at medically and financially compromised patients[12,13].

Zygomatic implants may be used as an alternative to bone grafts. Studies have shown that they are more predictable than alveolar crest augmentation techniques using autologous bone[14]. With a clinical survival rate as high as 96.7% (after 36 months of follow-up), zygomatic implants have proven their value in the past[14]; however, the success rate has been far less described. If mentioned, success was frequently based on scientific evidence found by researchers and not on the patient's perspective. The few studies that have analysed quality of life have not mentioned any grade of atrophy of the maxilla[14,16]. Only subjective classification using 'severe' and 'major' atrophy have been reported to justify the placement of zygoma implants, and thus the conclusions must be interpreted with significant caution. While the use of zygoma implants may be considered for the treatment of the severely resorbed maxilla, the known risks and complications associated with this approach cannot be ignored. Severe rhinosinusitis, infection, and fistula formation may arise, gravely affecting the oral health condition[15]. Zygoma implants should only be placed by well-trained clinicians with extensive experience. When complications arise, zygoma implants can be very difficult to remove and such removals are often accompanied by the loss of a significant amount of bone[15]. The latter effect could further compromise the patient's health because of the already low volume of bone in the maxilla. Zygomatic implant placement should always be regarded as a major surgical procedure. Furthermore, if removed, the installation can never be reused.

Regarding the AMSJI, a few fail-safes are built into the design[4]. Certain areas are specifically designed to be weak, facilitating cutting if any of the four arms should show any complication for which removal is necessary. If complete removal of the AMSJI is indicated, a replica can be three-dimensionally printed because the STL files are permanently stored in the database.

Patient satisfaction with the AMSJI rivals the mean satisfaction value of autologous bone augmentation procedures. Compared with AMSJI surgery, however, bony reconstruction of the atrophic maxillary crest entails several drawbacks, often not fully commented upon in the literature[17]. The anterior iliac crest and the calvaria are

preferred regions for harvesting[18]. Usually, the anterior and premolar zone of the maxilla are broadened with the harvested bone whilst in the molar zone, sinus floor augmentation is performed[19]. Often, two to three surgical procedures are required, the first being bone harvesting and transplantation and the second being implant placement, with the variable need for a third minor surgery for exposure of the submerged staged implants. Circular bone augmentation necessitates general anaesthesia entailing two operative sites including their potential complications[11,18,20]. Early resorption may result in an unesthetic and difficult to clean 'stilt house' in the anterior and premolar zone[21–22]. Torres et al. (2019) reported bone grafting success of 76% following iliac and calvarial bone augmentation in the anterior zone, from 5 to 15 years[23]. Bone loss or resorption are more frequently observed in horizontal augmentations than in vertical augmentations of localized defects[24]. Marginal bone loss increases over a period of 10 years before reaching a stable value[23]. Results are superior in the molar zone with sinus augmentation[25] and with calvarial bone as compared to iliac crest bone (11% vs 33% vertical resorption after 19 months on average in mixed mandible and maxillary crestal augmentations). Complications of crestal augmentation (partial and total dehiscence, graft loss) in the anterior zone are to be feared[26-28]. Schneiderian membrane perforation, as well as acute, chronic, and late-onset sinusitis are feared complications with sinus floor augmentation[29–30].

The provision of conventional endosseous implant therapy, which requires the scope of graft procedures and surgical staging as discussed, usually necessitates that the patient not wear a denture for a considerable period, resulting in compromised masticatory function. In some cases, a cemented provisional prosthesis may be placed on provisional implants during the bone healing phase, but this may be limited by the availability of bone[12]. In contrast, the AMSJI can readily be placed in the private clinic, and in medically comprised and/or elderly patients, without having to resort to a hospital, decreasing the burden for society (depending on national healthcare systems). In the case of total loss of an AMSJI, none of the anatomical structures have been damaged. The frame can be printed and if the soft tissues are well healed, the AMSJI can be installed again, whilst reusing the existing suprastructure and denture. This would be impossible in treatments that incorporate zygomatic implants, or the All-on-Four concept; with these treatments, the anatomy is unfavourably affected, and suprastructures and dentures would have to be manufactured de novo.

Excellent OHIP-14 scores were obtained for the patients who underwent AMSJI placement in this study. Both the mean overall OHIP-14 score, and the mean individual domain scores decreased over time, resulting in an overall mean OHIP score of 5.80 (SD 4.18) at 12 months (T3). Dahl et al. reported an OHIP-14 score of 4.1 in the Norwegian adult population (2441 patients)[31]. That the AMSJI score is only slightly worse in the current study patients could easily be explained by all 15 patients being orally compromised and aware of having very few options for obtaining fixed teeth. Many of them had experienced oral problems in the past, and some had already undergone several surgeries for oral rehabilitation. Their satisfaction with obtaining fixed dentures at the completion of their treatment directly impacted their perceived oral health condition and this explains why they reported a good OHRQoL.

Some patients might have had inaccurate pre-treatment perceptions concerning the AMSJI. At T0, several patients expected an (almost) perfect score based on the NRS. Some found it difficult to see their expectations met at T1. With severe oral compromise, prospective patients must understand that their situation is extremely complex and difficult to manage. Efficient communication is vital to address their desires and perhaps relay some unrealistic expectations. Fortunately, many patients appreciated the AMSJI, as demonstrated by the increased NRS scores at T2 and T3 compared with that at T1, in most cases even surpassing the preoperative score. In conclusion, the AMSJI is a valuable new alternative to treat extreme bone atrophy of the upper jaw.

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Ethical approval: All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Ethics committee approval was granted on May 5, 2019 (code B.U.N. 143201939806).

Patient consent: Informed consent was obtained from all individual participants included in the study.

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Chapter III: Radiographic evaluation of bone remodeling after additively manufactured subperiosteal jaw implantation (AMSJI) in the maxilla: A one-year follow-up study

Van den Borre C, Rinaldi M, De Neef B, Loomans NAJ, Nout E, Van Doorne L, Naert I, Politis C, Schouten H, Klomp G, Beckers L, Freilich MM, Mommaerts MY. Radiographic evaluation of bone remodeling after Additively Manufactured Subperiosteal Jaw Implantation (AMSJI) in the maxilla: A one-year follow-up study. J Clin Med. 2021 Aug 12;10(16):3542. doi: 10.3390/jcm10163542.

Abstract

Additively manufactured subperiosteal jaw implants (AMSJI) are patient-specific, 3D-printed, titanium implants that provide an alternative solution for patients with severe maxillary bone atrophy. The aim of this study was to evaluate the bony remodeling of the maxillary crest and supporting bone using AMSJI. Fifteen patients with a Cawood–Howell Class V or greater degree of maxillary atrophy were evaluated using (cone beam) computed tomography scans at set intervals: one month (T1) and twelve months (T2) after definitive masticatory loading of bilateral AMSJI implants in the maxilla. The postoperative images were segmented and superimposed. Fixed evaluation points were determined in advance, and surface comparison was carried out to calculate and visualize the effects of AMSJI™ on the surrounding bone. A total mean negative bone remodeling of 0.26 mm (SD 0.65 mm) was seen over six reference points on the crest. Minor bone loss (mean 0.088 mm resorption, SD 0.29 mm) was seen at the supporting bone at the wings and basal frame. We conclude that reconstruction of the severely atrophic maxilla with the AMSJI results in minimal effect on supporting bone.

Keywords: maxilla; implantation; subperiosteal; alveolar bone loss; printing; three-dimensional; Cawood–Howell

Introduction

Patients suffering from full edentulism have limited options for oral rehabilitation. Subperiosteal implants were introduced 80 years ago out of the need to improve stability and retention of full dentures in patients suffering from excessive ridge resorption [1]. At that time, cast frameworks and analogue radiographical imaging often led to inaccurate designs. The concepts of oral biology and stress shielding were not well understood at that time. Stress shielding is a phenomenon characterized by bone loss resulting from the decreased physiologic loading of the bone, which occurs due to the elimination of the usual stress on the bone. The altered mechanical environment caused by the implant's increased stiffness can disrupt the natural bone remodeling process, contributing to stress shielding and subsequent osteopenia.

While endosseous implants are known to achieve osseointegration with a high degree of predictability, their placement and longevity are dependent on sufficient bone quality and quantity. Availability of an ideal osseous support may be compromised by excessive resorption or loss of the alveolar processes secondary to disuse atrophy, trauma, or neoplasia, which can render installation of endosseous implants risky or sometimes impossible [3–5]. Progression of alveolar bone resorption may continue following placement of screw-type implants, both in instances of placement into native alveolar bone and placement into regenerated bone following grafting procedures [5,6].

With the rise of digital technology, fabrication of patient-specific implants (PSI) has become possible. Disruptive 3D printing technology has led to the revisitation of earlier concepts such as subperiosteal implants.

This has resulted in the innovation of the additively manufactured subperiosteal jaw implant (AMSJI) concept (CADskills BV, Ghent, Belgium). The AMSJI consists of two subunits (left and right). These are customized to the skeletal anatomy of each patient, based on a supplied CBCT data set. The subunits consist of two wings and a basal looped frame connecting the arms and the transmucosal posts. The wings are situated on the canine and zygomatic buttresses and are fixed in these locations using

osteosynthesis screws (Figure 1). Both subunits are connected intra-orally by a temporary connector, and later by a definitive primary matrix structure.

The AMSJI protocol constitutes a contemporary solution for a select group of patients with inadequate bone stock for screw-type endosseous implants (Figure 1) [7]. This tailor-made concept not only allows fixation onto the bone, but it also offers the patient an immediate functional restoration in a single intervention [8]. Clinical follow-up studies are necessary to confirm the efficacy of this contemporary concept.

The aim of this study was to evaluate the effect of reconstruction of the severely atrophic maxilla with the AMSJI on maxillary bone morphology in 15 patients.

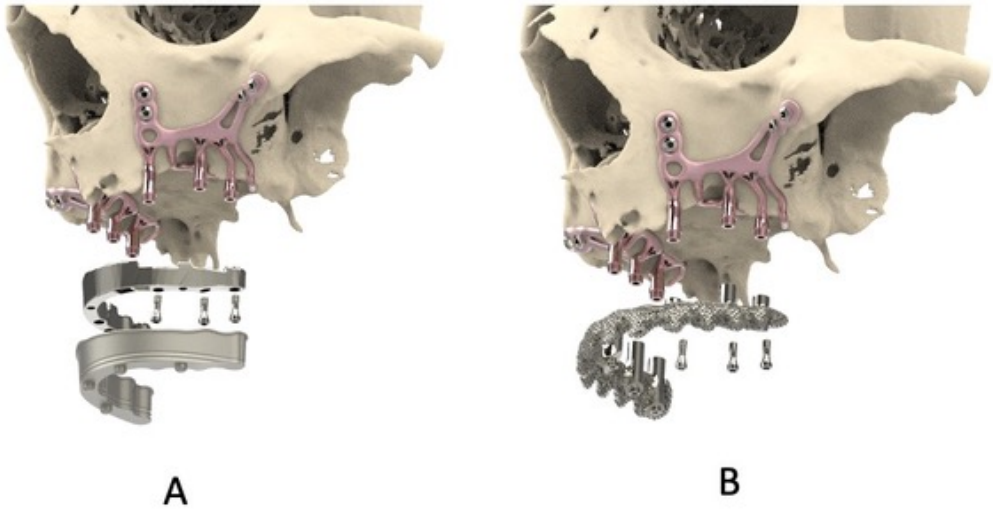

Figure 1. Visualization of the left and right AMSJI system and the connecting suprastructure. (A) The suprastructure consists of a double structure of an overdenture. (B) The suprastructure is a 3D-printed titanium scaffold of a hybrid bridge.

Materials and Methods

A multicenter prospective study was designed by the International Workgroup on AMSJI. Patients were included in the study who were deemed to have Cawood–Howell maxillary alveolar atrophy of grade V or higher and wished to have maxillary rehabilitation with a fixed prosthesis. All surgeons received training using model surgery before operating their first AMSJI patient or by having their first case assisted by an experienced AMSJI surgeon. Patients were excluded from the study if they or

the treating surgeon decided not to undergo a 1-year post loading CT scan, or if the CBCT was not a large enough dataset to allow full visualization of the AMSJI.

Perioperative antibiotic coverage consisted of amoxicillin–clavulanic acid, generally continued for five to seven days postoperatively.

Evaluation of the AMSJI position and effect on the surrounding bone was accomplished using CBCT imaging at one (T1) and twelve months (T2) after functional rehabilitation with the AMSJI. To ensure a consistently high quality of radiographic imaging, the following parameters were used: (1) conventional matrix: 512 rows x 512 pixels, (2) 90–120 kVp; (3) slice thickness was maintained between 0.5 and 0.7 mm, for CT, and 0.150 mm slice thickness for CBCT, and the same slice spacing was maintained throughout the scanning procedure; (4) each slice had the same display field, the same center of reconstruction, the same direction, and the same table height; (5) feed per rotation: max 1.0 mm; (6) reconstructed slice increment: maximum 1.0 mm; (7) the reconstruction algorithm for the bone was set at high resolution; and (8) Gantry tilt: 0°. All the images were anonymized. Patients who were included as subjects in the study were assigned a code.

Postoperative CBCT images were stored as DICOM datasets. Data were imported into Materialise Medical 22.0 (Materialise, Leuven, Belgium) for segmentation. A threshold was chosen by the first author based on the suggested predefined threshold sets for “bone”. A 3D model was then generated. Semi-automated segmentation of the 3D model was established using a “region grow mode”, which was a feature of the analytical software. Manual 2D multi-slice segmentation was additionally performed to ensure meticulous removal of all titanium alloy and scatter. The final files were saved in stereolithographic (STL) format using a “calculated part”. An “optimal or high quality” was selected. The STL files were imported into Geomagic Studio 2018 (Geomagic, Morrisville, USA). Surface-based super-impositioning of the postoperative CT scans was carried out. Image fusion between the T1 and the T2 scan was obtained using a semiautomated registration process. Initial approximation was done by a manual overlap of the two images to achieve the best possible fit. Using the registration tool, images were aligned using the best-fit surface automatic alignment. With this method the software calculated the least possible distance between

the two scans being compared, resulting in an automatic overlap of the scans to achieve the best fit based on the closest points.

Data were then again stored in STL format and imported in Gom Inspect Suite (Zeiss, Oberkochen, Germany). A color-code model was automatically generated for each patient to visualize the differences over time of bone apposition and resorption. Selected points on the color-code mask show the discrepancy (mm) between the fused images. On the crest, six bony reference points (A–F) were chosen in the axis of the posts (Figure 2). Four more reference points (G, K, L, P) were chosen between the two screws of the AMSJI wings on both sides (Figure 3). These points were determined based on, respectively, the perpendicular location of the posts projected on the crest and by determining the middle between the two screw holes. To assess the bone quantity perpendicularly underneath the basal looped frame, six more reference points were chosen between the connection of the neighboring posts and the looped frame (H-J; M-O, Figure 3)).

Inter-rater reliability (parameters: single rater, consistency-agreement, two-way mixed-effects) and intra-rater reliability (two-way mixed-effects model) were calculated. The data were analyzed using SPSS version 27 (SPSS Inc, Chicago, IL, USA).

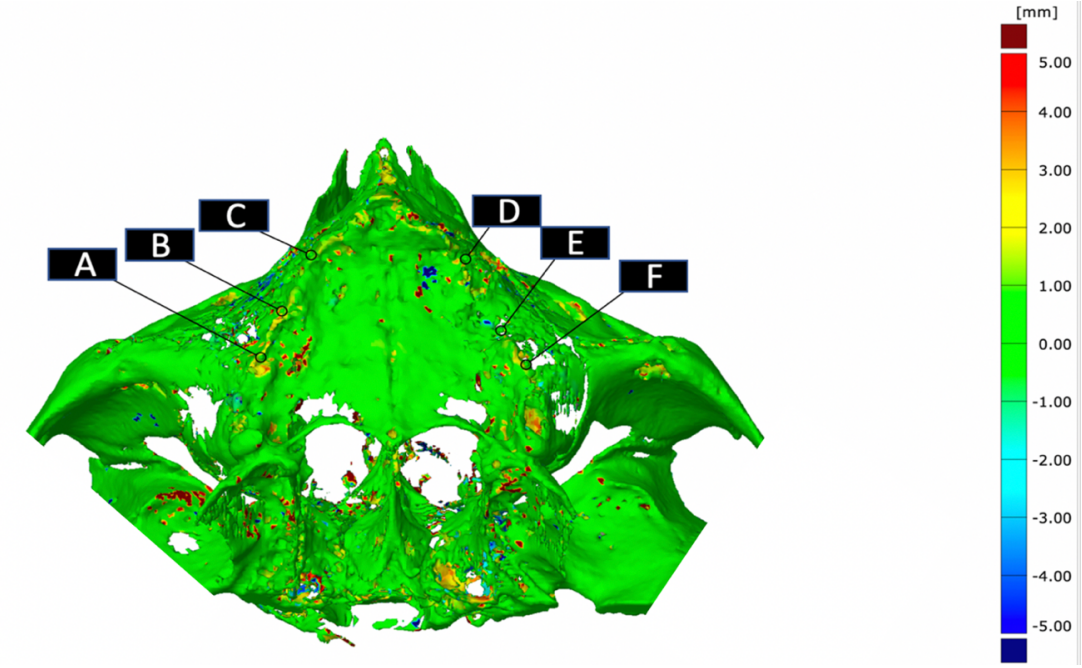

Figure 2. Bony surface reference points in the axis of the post. A- F indicates the reference points under the posts. The colour schematic indicates the discrepancy (mm) between the fused images.

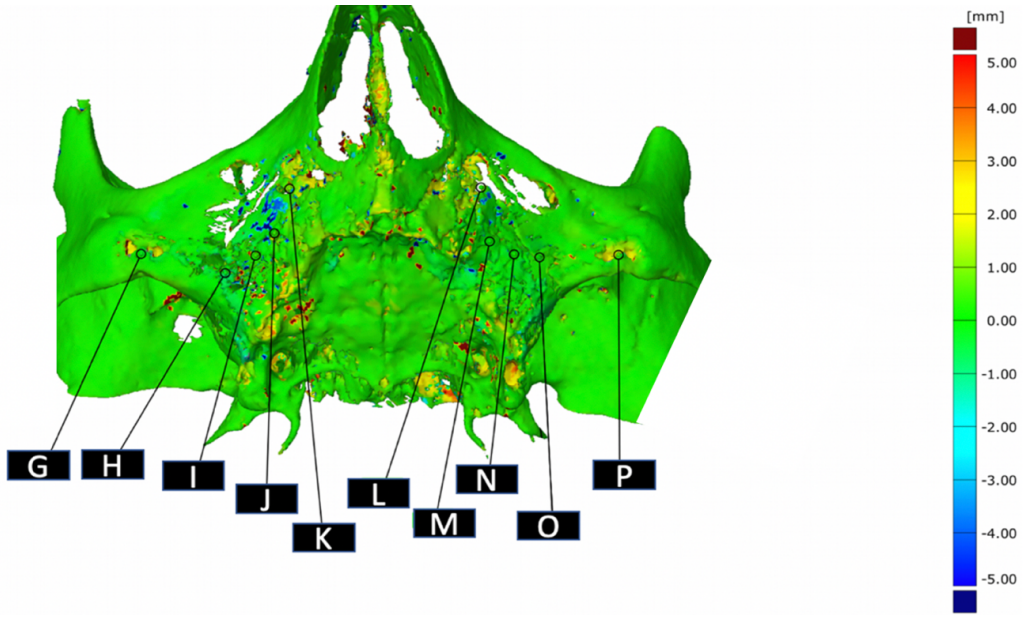

Figure 3. G, K, L, P: reference points under the wings; H, I, J, M, N, O: reference points under the basal looped frame.

Results

Nine males and six females with a mean age of 63.70 (SD 4.85) years were enrolled in this study. None of the patients complained of any discomfort, and none of the clinicians involved reported any complications at T1-T2. Surgeons and dentists were acquainted with implantology and charted results for both subjective and objective parameters. Objective and subjective parameters for success are the subject of another prospective study of the same International Study Group.

The status of the opposing mandibular dentition varied amongst subjects: two patients had a natural full arch dentition, and two had an interrupted arch without oral rehabilitation. Two additional patients had an interrupted natural arch with singular implants to replace lost molars. A fixed full arch prosthetic rehabilitation was observed in five patients. One patient had a fixed prosthesis supported by two mandibular AMSJIs and two singular implants at the canine regions. Three patients had removable frame prostheses.

No infections were reported at the time of recording. A total mean bone resorption of 0.26 mm (SD 0.65 mm) was seen over six reference points on the crest. Almost no bone loss (mean 0.088 mm resorption, SD 0.29 mm) was seen at the supporting bone at the wings and basal frame. Neutro-occlusion was established in each case. Tables

1 and 2 report resorption and apposition of bone at the reference points. Intraclass correlation coefficient (test–retest; two-way mixed effects model, type "consistency") was 0.86, indicative of good reliability. Interclass correlation coefficient (two-way random, 95%interval, type" consistency") had an average value of 0.91 with a 95% confidence interval equal to 0.73–0.97, also showing good reliability between the assessors [9].

Table 1. Effect on the alveolar crest underneath the posts after AMSJI rehabilitation

AMSJI	*Point*	Δ *Each Point T1-T2 (SD)*	Δ *Side T1-T2 (SD)*	Δ *AMSJI Total T1-T2 (SD)*
Right	A	-0.29 (1.04)	-0.24 (0.85)	-0.26 (0.65)
	B	-0.24 (0.94)		
	C	-0.18 (0.80)		
Left	D	-0.33 (0.89)	-0.27 (0.53)	
	E	-0.46 (0.57)		
	F	-0.050 (0.55)		

Effect on the bony alveolar ridge perpendicular underneath the posts (in mm). A negative value indicates a mean resorption.

Table 2. Effect on the underlying zygomaxillary bone after AMSJI rehabilitation

AMSJI	*Point*	Δ *each Point T1-T2 (SD)*	Δ *Side T1-T2 (SD)*	Δ*AMSJI Total T1-T2 (SD)*
Right	G	0.32 (0.67)	−0.060 (0.40)	−0.088 (0.29)
	H	−0.040 (1.46)		
	I	−0.38 (0.71)		
	J	−0.18 (0.57)		
	K	−0.03 (0.57)		
Left	L	−0.18 (0.41)	−0.11 (0.26)	
	M	−0.44 (0.47)		
	N	0.010 (0.59)		
	O	0.060 (0.75)		
	P	−0.030 (0.58)		

Effect of the AMSJI wings and basal frame on the underlying zygomaxillary bone (in mm). A negative value indicates a mean resorption, and a positive value indicates a mean apposition.

Discussion

Long-term survival of conventional subperiosteal implants has been documented [10–12]. Several reviews have, however, also reported on complications such as infections, early and late implant exposure, bone resorption, fistulation, and implant mobility, leading to considerable patient discomfort and implant failure [10–15]. The endosseous implants overcame several problems that had been experienced with the initial forms of subperiosteal implants and showed superior long-term results with minor patient discomfort [13–16]. Due to the feasibility of manufacturing in large quantities and the ease of installation and removal in the event of failure, endosseous implants became the first treatment of choice in the 1980s.

Despite their benefits, however, endosseous implants cannot be relied on by the surgeon to treat every clinical scenario. Adequate bone volume and quality are necessary to correctly position endosseous implants [17]. If sufficient bone volume and quality are not present, the endosseous implant is prone to fail, may damage important structures, or may be impossible to install [18]. The use of narrow and short implants

represents an alternative option, but if significant bone volume is lost in height and width, even these cannot be used [19]. Various regenerative techniques may be performed to augment the alveolar ridge in both the vertical and horizontal dimensions if insufficient bone volume precludes implant placement; however, this option is limited to cases where sufficient native bone exists to support the grafts. Autologous bone harvesting can be accomplished from a variety of anatomic sites, allowing for placement of onlay grafts. This approach is often used and is considered by some authors as the gold standard of regeneration techniques [20–22].

One of the main drawbacks to the utilization of free grafts is that during harvesting microcirculation is unavoidably severed, impeding reestablishment of graft circulation. Revascularization of the graft must occur to ensure osteogenesis and graft survival. This process requires time, during which osteocyte vitality is frequently compromised [23]. Consequently, small areas of dead bone will form, leading to undesirable and unpredictable graft resorption. The amount of resorption is strongly dependent on the site from which the bone was harvested. According to the literature, mandibular block grafts utilized for maxillary ridge augmentation have resorption rates between 5 and 28% [22,24,25]. Onlay grafts harvested from the iliac crest have been shown to exhibit 50% average volume decrease 6 months following placement in the atrophied maxilla [26]. Fourcade et al. (2019) investigated the resorption of calvarial (parietal) and ramic bone grafts for pre-implant reconstruction of maxillary alveolar ridges and found a mean resorption of 25% for both types of block grafts [27].

Guided bone regeneration (GBR) is frequently performed with bone graft procedures to mitigate these high resorption rates. With this approach, bone substitutes and membranes are used in addition to harvested autologous grafts to exclude non-osteogenic cell populations. As a result, osteoblast cell proliferation is promoted, and connective tissue and epithelial cells are mechanically excluded, resulting in lower resorption rates and higher bone volume following ridge augmentation [28,29].

Despite the reported variable rates of bone graft resorption, the success ratios following implant placement in grafted bone are high. Aghaloo et al. (2016) performed a literature review evaluating implant outcomes following bone grafting of completely edentulous maxillae [22]; 2446 implants were placed, with follow-up ranging from 1

to 12 years. The range of implant survival rate in this review was 73.3–100%. When GBR was performed, the reported survival rate improved to 96.1–100%. Motamedian et al. (2016) found a success rate between 72.8% and 100% of 2.647 implants when onlay grafting was performed using autologous blocks in an atrophied maxilla [30].

In addition to onlay grafting and guided bone regeneration, maxillary sinus floor elevation remains a popular method for augmenting bone volume; however, this is a technique-sensitive procedure. A frequent reason for failure is intraoperative rupture of the Schneiderian membrane. This is a common occurrence, with a reported incidence of perforation ranging from 3.6% to 41.8% [31]. If lacerated, the membrane cannot perform the function of graft containment, which impedes osteogenesis [32].

Augmentation of the maxillary sinus floor limits the anterior extent of maxillary reconstruction to the premolar level. Atrophied maxillae often present with severe ridge atrophy at the premaxillary region as well, and this aspect of the deficient ridge is often not amenable to augmentation. Despite this limitation, several studies have claimed high implant success rates (>90%) with follow-up periods from 1 to 11 years [22,33].

Bone regenerative techniques give excellent results in the context of long-term implant success in the atrophied maxilla; however, there remain several disadvantages to this approach. Bone augmentation relies on osteogenic potential, which varies among patients. This potential diminishes with age, which could lead to a higher degree of resorption [34]. If substantial resorption occurs, esthetic and functional stability of the implants can be influenced. This may necessitate repetition of bone augmentation to ensure proper volume for re-implantation. There is also a relevant morbidity associated with the harvest and installation of block grafts at both the donor and recipient sites. The risk of dehiscence, infection, pain, swelling, neurosensory deficits, and graft failure remain pertinent [35]. In addition, the harvested blocks remain of finite thickness, rendering complete augmentation of a severely atrophied maxilla difficult. A staged approach may be necessary to increase the potential for implant survival.

Aghaloo et al. (2016) showed that simultaneous graft-implant placement results in an implant survival ranging from 73.7 to 91% compared with 88.9–100% when a staged approach was used [22]. Staging of procedures carries the requirement for, and disadvantages of, multiple surgeries, with twice the risk for post-surgical complications to arise. Following bone augmentation, patients need to be encouraged to limit usage of dentures due to increased risk of wound dehiscence, graft displacement, and graft resorption if early loading is permitted prior to graft incorporation. This encumbers the patient to remain edentulous between surgical treatments for up to 4 months [22].

The advent of titanium 3D printing and 3D planning software made reconsideration of the subperiosteal implant concept possible. CBCT imaging depicts a patient's residual bone volume with considerable accuracy. CBCT data are used to generate a virtual bone model using reconstruction software. This facilitates the design of a subperiosteal implant with a high degree of accuracy for each patient.

Titanium (Ti) and its alloys are known to have excellent biocompatibility and are therefore widely used in medical and dental devices. This is in contrast with Vitallium (a cobalt–chromium–molybdenum alloy) used in the earlier lost-wax-technique subperiosteal implants, which has no soft tissue or bone integration properties. Bone resorption underneath rigidly fixed titanium alloy osteosynthesis plates is barely seen in the craniomaxillofacial skeleton [36]. Over 25% of osteosynthesis material used in both trauma and orthognathic surgery is overgrown by bone over time [36,37]. Such a phenomenon could contribute to an increase in stability and osseointegration of the AMSJI at the wings and basal frame. In our patients, sites of bony overgrowth were observed, predominantly at the upper parts of the wings. Beam hardening artefacts did not allow quantification.

Physiological alveolar ridge resorption in completely edentulous patients has been well documented [38–40]. The rate of resorption varies between patients, and strong variance of resorption has been shown at different times and sites within individual patients [41].

Initially, rapid bone loss occurs three months after tooth loss. This is followed by a slow but continuous resorption throughout life [40]. A systematic review and meta-

analysis performed by Koodaryan and Hafezeqoran (2016) reported an average early bone loss associated with maxillary and mandibular implants of around 1.5 mm during the first year after the final restoration was installed [42]. A mean annual bone loss of 0.2 mm thereafter was seen. We anticipate that a similar trend of bone loss can be expected with AMSJI beyond the first year of function. Patients who received AMSJI-supported prosthetic rehabilitation showed a mean resorption at the alveolar ridge of 0.26 mm (SD 0.65 mm) and 0.088 (SD 0.29) mm at the wings and basal frame on the underlying zygo-maxillary bone one year post loading.

The amount of resorption is dependent on several variables. One of the factors that can contribute to this loss of bone is the type of oral rehabilitation [19]. Kovacić et al. (2010) measured the bone resorption at the maxillary alveolar ridge using radiographic measurements on lateral cephalograms in 31 completely edentulous individuals after five years of wearing complete dentures [41]. A mean bone loss of 0.79 mm was found over a period of 5 years. Atwood et al. (1971) found the mean alveolar ridge resorption to be around 0.010 mm per year; however, the general rate of resorption varied greatly between different individuals from 0 mm to 0.70 mm [43]. This phenomenon can account for some of the crest resorption seen in our series.

Another factor that could account for some resorption is the raising of the mucoperiosteal flap [44–46]. When alveolar bone becomes exposed, the underlying bone is partially deprived of oxygen, and osteoclastic activity is thereby promoted, resulting in bone resorption and subsequent remodeling [47,48]. For implantation of AMSJI, preparation of a mucoperiosteal flap is necessary to correctly fixate the system.

Maier FM (2018) studied the effect on crestal bone in the maxilla after implant placement using conventional mucoperiosteal flap elevation versus a flapless procedure [49]. After one year, a mean crestal bone loss of 0.55 ± 0.57 mm was seen in the conventional mucoperiosteal flap group (100 patients vs. 95 in the control group). Merheb et al. (2014) came to almost the same conclusions and found a mean resorption of 0.40 mm after full thickness flap elevation [48].
To accurately perform a fusion of the T1 and T2 images, and to visualize the effect of AMSJI on the underlying bone, a segmentation of the AMSJI from the underlying bone on the CBCT images was necessary prior to the fusion.

Several software packages are available, which in turn use different tools for segmentation; however, the principle remains the same. The stored DICOM file is imported into the chosen program, and the desired anatomical structures are 3D-rendered towards a 3D model. A threshold is manually chosen initially to segment out any unvoluntary voxels. Thresholding defines a range of grey values. If voxels fall into this range, they are included in the segmented object. This is done manually. After determining the threshold and visualizing the underlying skeleton, further segmentation is done manually to filter out scatter. If segmentation is inaccurate, an error is already incorporated into the surface and volume before effective analysis can commence. Machine learning could improve the segmentation process, and further automation could lower the risk of operator error hereby improving segmentation and analysis results [50].

The AMSJI remained a challenge for segmentation of the CBCT data due to several factors: (1) some patients showed low bone quality, which made it difficult to visualize the bone as a 3D model; (2) the Ti-alloy composition of the AMSJI causes beam hardening artefacts; (3) the presence of bordering soft tissue; (4) low contrast resolution of several of the CBCT datasets; and (5) reduced quantity of the underlying bone present in some cases. This method of semiautomated segmentation, including the factors listed above, rendered the measuring process potentially prone to operator error. In addition, a surface-based superimposition uses only the surface of the 3D structure for the overlapping. A high-quality surface is required for an accurate superimposition [51].

Conclusions

In this study, 15 patients were radiographically examined 1 and 12 months after masticatory rehabilitation based on bilateral AMSJI implantation in the maxilla. The effect on the supporting bone was evaluated. Minor atrophy was seen at the alveolar ridge, but minimal atrophy was detected under the fixation wings.

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Chapter IV: Patient satisfaction and impact on oral health after maxillary rehabilitation using a personalized additively manufactured subperiosteal jaw implant (AMSJI)

Van den Borre C, De Neef B, Loomans NAJ, Rinaldi M, Nout E, Bouvry P, Naert I, Mommaerts MY. Patient Satisfaction and Impact on Oral Health after Maxillary Rehabilitation Using a Personalized Additively Manufactured Subperiosteal Jaw Implant (AMSJI). J Pers Med. 2023 Feb 8;13(2):297. doi: 10.3390/jpm13020297.

Abstract

Subperiosteal implants (SI) were first developed by Dahl in the 1940's for oral rehabilitation in case of severe jaw atrophy. Over time, this technique became abandoned due to the high success rate of endosseous implants. The emergence of patient-specific implants and modern dentistry allowed a revisitation of this 80-year-old concept resulting in a novel 'high-tech' SI implant. This study evaluated the clinical outcomes in forty patients after maxillary rehabilitation with an additively manufactured subperiosteal jaw implant (AMSJI®). The oral health impact profile – 14 (OHIP-14) and numerical rating (NRS) scale were used to assess patient satisfaction and evaluate oral health. In total, fifteen men (mean age 64.62 year, SD ± 6.75 year) and twenty-five women (mean age 65.24 year, SD ± 6.77 year) were included, with a mean follow up time of 917 days (SD ± 306.89 days) after AMSJI installation. Patients reported a mean OHIP-14 of 4.20 (SD ± 7.10) and a mean overall satisfaction based on the NRS of 52.25 (SD ± 4.00). Prosthetic rehabilitation was achieved in all patients. AMSJI is a valuable treatment option for patients with extreme jaw atrophy. Patients enjoy treatment benefit resulting in a high patient's satisfaction and impact on oral health.

Keywords: 3D-printing; subperiosteal; implant; patient satisfaction; alveolar bone loss; patient specific implants

Introduction

Masticatory rehabilitation of the severely atrophied maxilla has always been a difficult problem. Historically, preprosthetic surgical techniques, including absolute and relative augmentation, have been used to improve retention of traditional removable dentures. Dahl developed the subperiosteal implant (SI) to support the denture and improve masticatory function [1]. However, these ‘classical’ subperiosteal implants did not enjoy a good reputation. Reasons of failure were plentiful. Vitalium®, a cobalt chrome alloy that is inert in human tissue was used in the form of a frame; sometimes resection of keratinized mucosa was performed around the tissue piercing posts and over-the-mucosa impression techniques were performed, leading to an inadequate fit of the SI [1-2]. As a result, poor osseointegration occurred in addition to soft tissue dehiscence, pathological pocket formation and infection, ultimately leading to the failure of the entire SI-system, leaving large bone defects.

To improve survival and success rates, many changes have been made to the technique and design of SIs over the years, affecting both the subgingival and supragingival structures. The emergence of modern dentistry improved medical imaging and fitting, 3D printing of titanium and better material knowledge enabled a revision of the 80-year-old concept of subperiosteal, resulting in a new 'high-tech' subperiosteal implant [3-4]: the additively manufactured Subperiosteal Jaw Implant (AMSJI) (see Figure 1). AMSJI is a patient-specific, custom 3D-printed implant for immediate functional recovery with just one procedure under local, sedation or general anesthesia. Patient-specific SIs are emerging again and are now regularly used in clinical practice [5-7]. Several long-term data have been published on the survival rates of traditional SIs [8-9]. However, the patient perspective was often not considered and studies evaluating patient-related outcome after SI are rare. One study reported excellent results at 1 year in a small group of maxillary AMSJI patients with limited follow-up [10]. High patient satisfaction is an essential goal to be achieved in oral rehabilitation. By measuring patient-related outcomes, the true treatment benefit (patient satisfaction) can be evaluated and therefore cannot be ignored. The aim of this study was to collect data on patient-reported satisfaction and to score the impact on oral health in patients with AMSJI in the severely atrophic maxilla in a larger

group of patients, treated by experienced surgeons, with a follow-up in the medium term, and to compare it with current commonly used methods of oral rehabilitation.

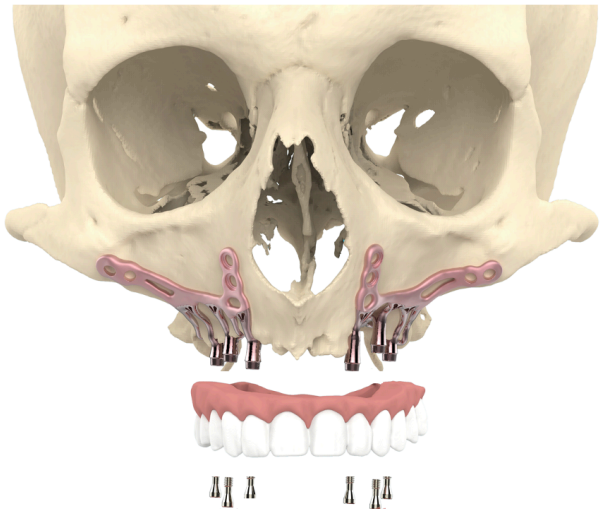

Figure 1. Visualization of the patient specific, AMSJI for the maxilla

Materials and Methods

An international multicenter study was set up and included a total of 40 patients of which 31 Belgian, 5 Italian and 4 Dutch patients. Surgeons experienced in the technique with more than five patients treated with the AMSJI were approached to participate in the study. Inclusion criteria were all patients who underwent bilateral maxillary AMSJI placement at least one year ago. In total, 122 patients were eligible for inclusion, however, the number was limited by patient and surgeon decisions to enroll in this retrospective study. All AMSJI's were placed for maxillary severe atrophy (Cawood-Howell classification 5 or higher). Maxillary defect reconstructions were excluded no other exclusion criteria were used.

All patients were evaluated using a survey that was anonymized using a "patient code". This is randomly chosen and not linked to the patient or hospital. Broad demographic information was obtained alongside subjective data on patient satisfaction and impact on oral health. Two questionnaires were used:

A. The Oral Health Impact Profile – 14 (OHIP-14)

The OHIP-14 includes seven domains related to functional limitations, physical pain, psychological discomfort, and physical, psychological, and social disabilities. Each domain consists of two questions scored on a five-point scale: 0, never; 1, almost never; 2, occasionally; 3, often; and 4, very often or every day. Domain scores were obtained by summing the answers to the two corresponding questions. Total scores were derived by summing all scores of all 14 questions. The score can range from 0 to 56 with domain scores from 0 to 8. The higher the OHIP-14 score, the worse the oral health-related quality of life (OHRQoL).

B. Numerical Rating Scale (NRS)

The NRS is based on the visual analog scale (VAS) and aims to provide greater insight into aesthetic benefit, chewing, comfort, phonetics, cleaning, and overall satisfaction. This scale consists of six questions with an eleven-point scale ranging from "0" for "not at all satisfied" to "10" for "very satisfied". Adding the scores from all six questions results in a total score that can range from 0 to 60, where 0 is the worst and 60 is the highest possible satisfaction score.

Statistical analysis

The data were analyzed using SPSS version 26.0. (IBM, New York, USA) for Mac OSMojave. The means and standard deviation were calculated for the OHIP-14 scores and NRS test. Each domain and question were also evaluated separately.

Results

Fifteen males (mean age 64.62 years, SD ± 6.75 years) and twenty-five females (mean age 65.24 years, SD ± 6.77 years) with a mean follow-up period of 917 days after AMSJI installation (SD ± 306.89 days) were included in this study. Final restoration of the prosthesis was successful in all patients and all patients presented with their fixed or removable prosthesis in use at the time of consultation. There were 12 patients with postoperative inflammation (i.e., swelling, marked redness, pain...).

All were initially treated with antibiotics. Due to apparent soft tissue infection, drainage, exploration and/or mechanical debridement was performed in 6 of these patients. In three patients, a post had to be removed due to persistent and uncontrollable infection (see Figure 2 and 3). The stability of the AMSJI implant or prosthetic restoration was not compromised in these patients. At the time of examination, all but one of the AMSJI implants were firmly fixed (mobility of > 1 mm after removal of the final restoration). Partial exposure of the arms was observed in 26 patients. However, patients did not experience this as a functional or aesthetic impediment. Total OHIP-14 was calculated to give an overall picture at the time of interview. A mean value of 4.20 was calculated (SD ± 7.09). Evaluation of each domain was performed separately (see Table 1). Patients reported a mean NRS scale value of 52.25 (SD ± 4.00). Mean scores based on each domain/question separately were also calculated, given a more thorough representation (see Table 2). Graphic representation of the data set for OHIP-14 and NRS scale is given in figure 4.

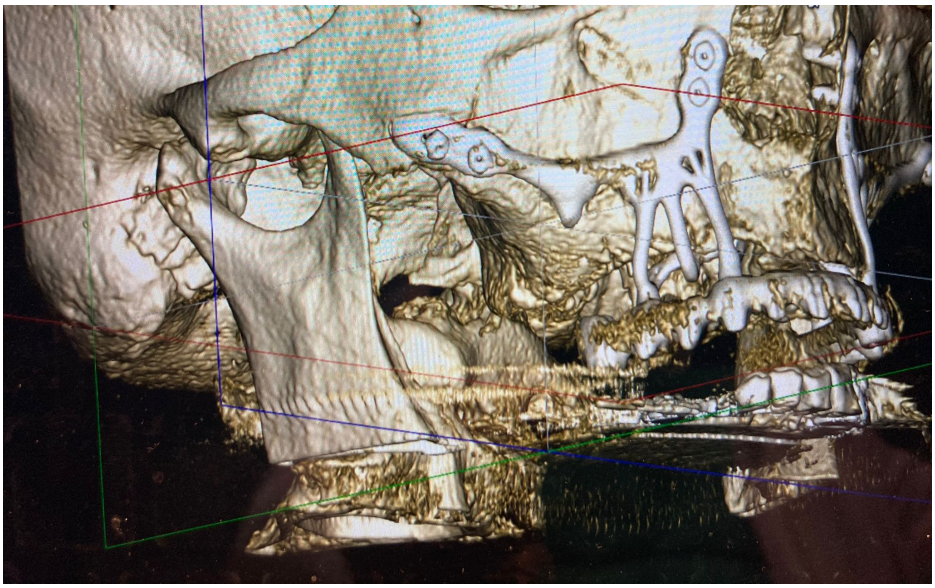

Figure 2. Cone beam computed tomography and three-dimensional reconstructed image of one of the patients where the distal arm of the right AMSJI had to be removed due to persisting infection

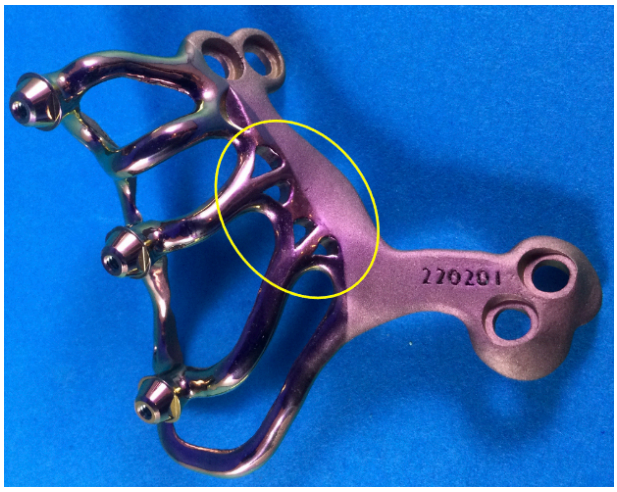

Figure 3. Picture of a right AMSJI with detailed visualization of the branched structure (yellow circle) connecting the basal looped frame with the arms and posts. In case of uncontrolled infection, a post can be easily removed without affecting the other arms be cutting the branches.

Table 1. Results of the Oral Health Impact Profile-14 (OHIP-14)

Domain	Mean	SD
Overall OHIP-14	4.20	7.09
1. Functional limitation	1.08	1.51
2. Physical pain	1.00	1.75
3. Psychological discomfort	0.75	1.45
4. Physical discomfort	0.53	1.20
5. Psychological disability	0.38	1.13
6. Social disability	0.25	0.84
7. Handicap	0.23	0.73

SD, standard deviation; The overall OHIP-14 is given together with values of each domain separately. A low mean OHIP-score of 4.20 (SD ± 7.09) was calculated, indicating a high oral health-related quality of life.

Table 2. Results of the Numerical Rating Scale (NRS)

Question	Mean	SD
Overall NRS	52.25	4.00
1. Aesthetic benefit	9.03	0.92
2. Chewing	8.83	1.11
3. Comfort	8.63	1.29
4. Phonetics	8.48	1.38
5. Cleaning	8.73	1.28
6. General satisfaction	8.58	1.11

SD, standard deviation; The overall NRS is given together with values of each question separately. A high mean NRS-score of 52.25 (SD ± 4.00) is seen, indicating a high patient satisfaction.

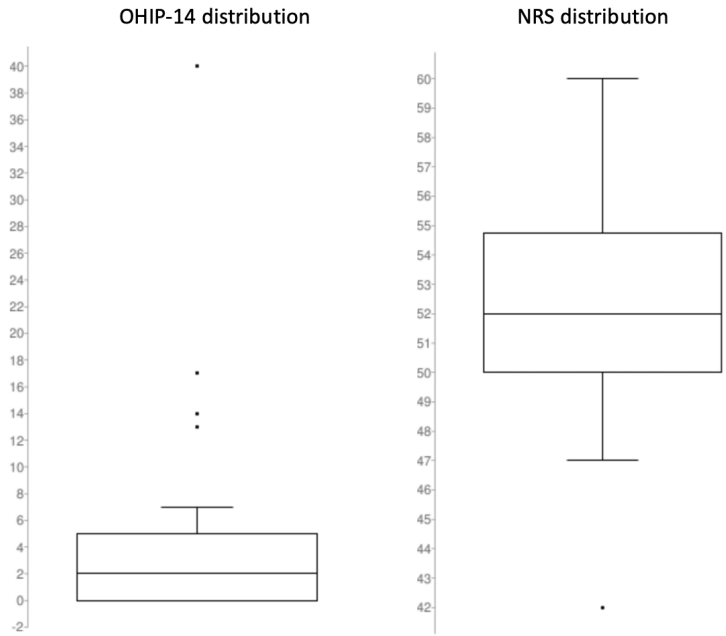

Figure 4. Visual representation of the distribution of the data set of the OHIP-14 and NRS score.

Left: The boxplot of the OHIP-14 values ranges from 0 (first quartile) to 5 (third quartile). Median value is 2 and interquartile range is 5. Minimal and maximal values were respectively 0 and 40 with 40,17,14 and 13 being the outliers.

Right: The boxplot of the NRS values ranges from 50 (first quartile) to 54.75 (third quartile). Median value is 52 and interquartile range is 4.75. Minimal and maximal values were respectively 42 and 60 with 42 being the only outlier.

Discussion

Complete edentulism has been a major problem since the dawn of time and is often described as the “final marker of disease burden for oral health” [11] Although the prevalence of edentulism has decreased in recent decades, it is still considered a major problem worldwide [12]. One of the associated problems of edentulism is the significant effect on residual ridge resorption. The alveolar ridge of patients who remain edentulous for a long time will become vestigial due to bone resorption [13]. This process is further enhanced by the adverse forces created when loading the jaws with soft tissue supported dentures [14]. Continued resorption can result in ill-fitting dentures, leading to retention problems that compromise mastication and speech, and cause functional and sensory disturbances in the oral mucosa, salivary glands, and musculature [15]. Oral rehabilitation using endosseous implants has become a standard treatment option. However, due to severe resorption, placement of endosseous implants is not always possible. Autologous bone augmentation techniques represent the “gold standard” for restoring alveolar ridge bone volume. One of the preferred donor sites, in case of reconstruction of large deficiencies (as is the case with a Cawood Howell Class V or more), is the iliac crest.

Gjerde et al. (2020) assessed patient-reported outcomes in 44 patients (mean age of 61.2 years ± 13) after maxillary alveolar ridge augmentation with anterior iliac crest grafting. An OHIP-14 score of 8.4 ± 9.7 has been reported [16]. The functional disability domain scored the highest (2.34) and the social disability domain scored the lowest (0.61). This is in accordance with our study. “Functional limitation” (1.08) and “Physical pain” (1.00) were indeed graded the highest. One of the main reasons was that a limited number of patients still had minor pronunciation problems. Non reported with painful aching, however some still needed some adaptation time to get used to their final prosthesis. Social disability (0.25) and handicap (0.23) scored the lowest as almost none of the patients reported any signs of being more irritable with other people because of their AMSJI installation. None of the patients reported any decrease in life satisfaction at time of investigation.

Calvarial bone serves as a valuable alternative to iliac crest bone. Wortmann et al. (2022) conducted a meta-analysis and compared patient-reported outcomes after

autogenous iliac bone or calvarial bone harvesting in orally compromised patients [17]. They found patient-reported satisfaction with a median VAS score ranging from 8.8-10 in 206 patients after calvarial bone augmentation. For anterior iliac bone grafts, 696 patients were enrolled, and overall patient satisfaction was reported: the median VAS score ranged from 9.5 to 10. No statistical difference was found when two techniques were compared.

Patient-related outcome measures for AMSJI are comparable to the average satisfaction rates of autogenic bone augmentation. However, AMSJI requires only one surgical procedure and provides immediate postoperative chewing function. This contrasts with bone regeneration techniques that use a two-step protocol. The first augmentation must take place and endosseous implants cannot be placed until three to four months later. That is, if resorption of the graft has not occurred. Time is then required for the implants to integrate into the bone, further delaying the final placement of the prosthesis. Between stages, patients are advised not to wear dentures for a period in order not to compromise the graft and to ensure proper healing. Another drawback is that harvesting extraoral bone grafts for ridge augmentation is complex to perform and very technique dependent. Gjerde et al. (2022) reported only 70.1% implant survival along with prosthetic rehabilitation after 1 year. Two patients (4.7%) reported that their oral health deteriorated after treatment. Three patients (7.30%) reported walking difficulties. Donor site pain was reported by 16 patients (38%) and lasted on average 18.10 ± 16.10 days. In addition, patients had an average of 4.3 days of hospitalization and 20.2 days of sick leave after iliac crest-derived alveolar bone grafting [16].

Another common option and alternative for rehabilitation of the atrophic maxilla are zygomatic fixtures. Several studies indicated a high success rate and predictability [18-21]. However, there are no clinically applicable criteria for success and the definition of "success" is used as a very flexible term. Most studies consider success to be the survival of the implants placed. Objective reporting of patient satisfaction and quality of life over time is often absent or even ignored when reporting outcomes. An exception is the study by Fernández-Ruiz et al. (2021). These authors examined the quality of life and satisfaction in 40 patients who were rehabilitated with fixed prostheses supported by a combination of zygoma fixtures and conventional implants

(anterior region) [19]. Patients' follow-up was 19.40 ± 4.37 months and a mean VAS of 18.48 ± 3.42 was reported. Although reasonably good patient satisfaction scores are reported, this article should be read with caution. A recent review of this article in the "Journal of Evidence-Based Dental Practice" found that this study has a high risk of bias, which minimizes the applicability of the results [22].

Compared to zygomatic fixtures and autogenous bone augmentation, AMSJI is a more patient-friendly alternative. Patients can be treated in an outpatient clinical setting with local anesthesia alone (for those who so desire). No hospitalization is required, and patients often report only mild pain that is easily controlled with first-line analgesics (acetaminophen and NSAIDs). Postoperative complications were seen. However, these cannot be compared to the major complications (i.e., penetration into the eye socket) that occur in some cases after placement of the zygomatic implant.

One of the limitations of this study is that no baseline value neither data before nor after SI installation were available as this is a non-prospective study. For this reason, it is not possible to compare or calculate any statistical difference before or after AMSJI installation. However, the goal was to evaluate patients' satisfaction and impact on oral health at the time of investigation and to compare these to current techniques. Few studies exist which calculate PROMS and OHIP-14 values in the general population. In a previous study by Dahl et al. (2011) an OHIP-14 score of 4.1 was seen in the general Norwegian adult population. Considering this as a representative value for the general population, the patients in our study reported almost equal OHRQoL [23]. The same was found by Wang et al. (2021) who evaluated patient satisfaction and quality of life related to oral health 10 years after placement of endosseous implants in a non-atrophied alveolar ridge [24]. They found that patients were almost as satisfied as the natural teeth population in terms of function and aesthetics. The low OHIP-14 and high NRS scores in our series may be explained by the fact that the included patients were all orally crippled and had almost no alveolar ridge to maintain a prosthetic construct. Patients were bound by relining sessions and denture adhesives to improve stability during normal functioning. Any improvement in function would likely have a major positive impact and OHRQoL. Most AMSJI patients had some rehabilitation problems in the past with various failed

augmentation techniques. It is therefore quite understandable that these patients are very satisfied to finally get permanent teeth.

Conclusions

Oral rehabilitation in patients with severe maxillary atrophy using a personalized AMSJI is a valuable treatment option. Although some complications were reported, patients enjoy treatment benefit resulting in a high patient's satisfaction and impact on oral health.

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Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: Prof. Dr. Maurice Mommaerts declares that he is innovation consultant at CADskills BV. All other authors report no conflict of interest.

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Chapter V: Soft tissue response and determination of underlying risk drivers for recession and mucositis after AMSJI implantation in the maxilla®

Van den Borre C, De Neef B, Loomans NAJ, Rinaldi M, Nout E, Bouvry P, Naert I, Van Stralen KJ, Mommaerts MY. "Soft tissue response and determination of underlying risk drivers for recession and mucositis after AMSJI® implantation in the maxilla". Int J Oral Maxillofac Implants. (in press)

Abstract

Purpose:

There are few treatment options for oral rehabilitation in patients with advanced maxillary resorption (Cawood-Howell Class V or more). Patient-specific, 3D-printed titanium subperiosteal implants have been described as a potentially valuable alternative solution. Surgeon and patient mediated functional outcomes have been studied and the results are promising. The surrounding soft tissue health has been much less researched. This study aims to evaluate the soft tissue response to the placement of additively manufactured subperiosteal jaw implants (AMSJI®) in the severely atrophic maxilla and to identify possible risk factors for soft tissue breakdown.

Materials and methods:

An international multicenter study was conducted and fifteen men (mean age 64.62 years, SD ± 6.75) and twenty-five women (mean age 65.24 years, SD ± 6.77) with advanced maxillary jaw resorption (Cawood-Howell Class V or more) were included in this study. General patient data were collected, and all subjects were clinically examined. Inclusion criteria were patients who underwent bilateral AMSJI placement® in the maxilla at least a year before and whose surgeon and themselves agreed to participate in the study before their inclusion.

Results:

A total of forty patients were enrolled with a mean follow-up period of 917 days (SD ± 306.89 days). Primary stability of the implant was achieved postoperatively in all cases, and all implants were loaded with a final prosthesis. At the time of study, only one patient showed mobility of the bilateral AMSJI (more than 1 mm). Exposure of the framework, due to mucosal recession, was seen in 26 patients (65%) and was mainly in the left (21.43%) and right (18.57%) mid-lateral region. Thin biotype and the presence of mucositis were found to be risk factors (p-value < 0.05). Although not significant, smokers had a nearly seven times (Odds ratio 6.88, $p=0.08$) more risk of developing a recession compared to non-smokers.

Conclusion:

Twenty-six (65%) patients presented with a recession in one or (more) of the seven regions after oral rehabilitation with bilateral AMSJI installation. Several risk drivers were evaluated. The collapse of soft tissues around the AMSJI that led to caudal exposure of the framework arms was correlated with a thin biotype and the presence of mucositis.

Key words: alveolar bone loss; jawbone; gingival recession; AMSJI, subperiosteal; printing, three-dimensional; risk factor; implant; tooth

Introduction

When compared to traditional removable complete dentures, implant-supported dentures—including either total overdentures or a hybrid prosthesis—significantly enhance patients' quality of life (1). Placement of endosseous implants (1) is considered the gold standard for prosthetic rehabilitation in a partially or fully edentulous patient. However, when advanced resorption of the jawbone occurs, insufficient bone width and/or height hinders the placement of endosseous implants. Several surgical techniques have been described for bone regeneration. Many believe that the ideal material for augmenting a highly maxilla is autologous bone taken from an extraoral site, more specifically from the calvarium and the iliac crest (2-4). For many patients and professionals, the invasiveness of the surgery, the wait of 3 to 4 months before fixtures are installed, and the unpredictable resorption to the original bone borders provide a challenge. However, these techniques are complex, costly, often involve multiple surgical steps, and can present a high percentage of complications (2). Non-regenerative strategies gained popularity, e.g., very short implants and extra-maxillary implants. (5,6)

In the past, subperiosteal implants (SI), another solution to the extremely atrophic maxilla, have shown unpredictable results. First described by Dahl in 1943, a subperiosteal implant is a type of frame placed between periosteum and jawbone (7). Over the years, many changes have been made to the technique and design of the SI that affect both the submucosal and the supra-mucosal structures. Computer-aided design/computer-aided manufacturing, material knowledge, titanium 3D printing, virtual stress-strain testing and improved knowledge of oral microbiology led to the emerging concept of a novel subperiosteal implant, the additively manufactured subperiosteal jaw implant (AMSJI) (8,9).

Although they reported stable results over a long period of time, several assessments reported early and late (partial) exposure of the traditional cobalt-chromium SI due to recession of the surrounding mucosa (10-12). With titanium classic endosseous implants, it is known that the peri-implant keratinized tissue has a major influence on the long-term stability of the implant, the aesthetic appearance, and the survival of the prosthetic reconstruction. The recession of the surrounding mucous membrane

can lead to the formation of persistent biofilm which can lead to mucositis. When left untreated, local inflammation worsens and gives rise to peri-implantitis with implant failure at the end. For SI, the value of the surrounding soft tissues is much less understood and studied. This study aims to assess soft tissue response to titanium AMSJI in the maxilla and identify risk factors for soft tissue recession.

Materials and methods

As part of an international multicenter study, surgeons with experience in the technique with more than five patients treated with AMSJI were approached to participate in the study. Inclusion criteria were patients who suffered from wearing dentures in the maxilla, due to severe bone resorption, Cawood-Howell classification V or more, and who were treated with AMSJI at least a year ago. Exclusions were disagreements of patients, surgeons, and dentists with the study. No other exclusion criteria were used. Eventually, forty Belgian, Dutch, and Italian patients were registered.

Data collection

All enrolled patients were interviewed and clinically evaluated during the consultation. A randomly chosen patient code was used to anonymize the data. General patient information was collected, including age, gender, ASA score, smoking and daily alcohol consumption. The patient's history was monitored with emphasis on the absence/presence of radiotherapy, the use of bisphosphonates, chronic periodontitis, cardiovascular/liver disease, diabetes, and oral parafunctions. Information about the type of prosthesis (hybrid or removable) and the use of an ostectomy guide during surgery was also collected.

In patient studies, mucosal recession and/or exposure of the framework were identified and schematized for data collection using Fig. 1.

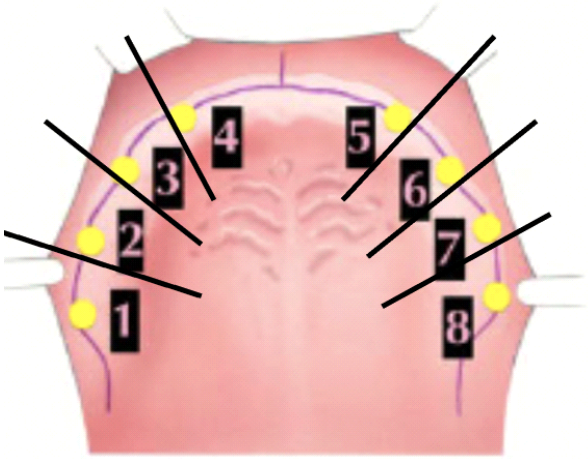

Figure 1. Schematic representation of the location of the posts in the upper occlusal view used for surgeons to indicate the location of the recession. Recession and/or exposure of the framework were schematized. A total of 7 regions can be determined. All recessions were indicated and categorized based on this figure.

The mobility of each unilateral AMSJI was manually evaluated and tested by the clinician. The degree of mucositis around the different poles or exposed frame (if any) of the AMSJI was evaluated using the Gingival index (GI) as described by Loe & Silness (1963) (13). Mucous membrane health was assessed using the four-point scale ranging from 0 to 3 (0, no inflammation; 1, slight color change and edema; 2, redness/enamel; 3, marked redness/inflammation/ulceration) for each post /recession. GI for the patient was calculated individually by dividing the total sum by the number of posts (n = 6). An average score was then given to describe the degree of mucositis (0: none; 0.1-1: mild; 1.1-2: moderate; 2.1-3: severe).

To evaluate the formation of biofilm, the modified plaque index (mPI) described by Mombelli et al. (1987) was used (14) This was also based on a four-point scale ranging from 0 to 3 (0, no detection of plaque; 1, plaque recognized by running a probe over the pole/frame; 2, plaque seen by the naked eye; 3, abundance of soft material). The mPi for the patient was calculated by dividing the total score by the number of posts. Each patient was then given a plaque score; 0: Excellent; Good: 0.1-0.9; Fair: 1.0-1.9; Poor: 2.0-3.0.

The phenotype of the mucous membrane was assessed using a periodontal probe. If the circumference of the underlying periodontal probe could be seen, it was categorized as thin (score: 0); if not, it was categorized as thick (score: 1).

All patients in this study had designed an AMSJI with six posts/connections (2-7) to allow for dental restoration. For this reason, no values have been calculated for items 1 and 8.

Statistical analysis

The data set was analyzed with RStudio version 2022.07.2 on Windows 11 (R foundation for statistical computing, Vienna, Austria). The mean and standard deviation (SD) values were calculated for age and implantation time. All risk factors were evaluated for clinical significance and a p-value was calculated together with an Odds ratio (OR).

Results

Fifteen men (mean age 64.62 years, SD ± 6.75 years) and twenty-five women (average age 65.24 years, SD ± 6.77 years) could be included. Their mean follow-up period was 917 days (SD ± 306.89 days).
Patients were usually classified as ASA I (n= 18) and ASA II (n = 21). Only one patient was ASA III. Ten people smoked and sixteen patients consumed alcohol daily. An ostectomy guide was used for seven patients. In twenty patients (n = 20) a thin phenotype was seen, the remaining twenty patients had a thick phenotype.

Primary stability of the bilateral AMSJI in the maxilla was achieved for each patient. At the time of research, all but one of the AMSJIs were rigidly fixed. The final prosthetic restoration was successful in all patients studied. Twenty patients received a removable prosthesis with double structure, while the other twenty patients received the hybrid non-removable prosthesis. The choice was made by the restorative dentist and the patient's preferences based on aesthetic and phonetic limitations.

Most patients (n=18) scored an "excellent" plaque index, meaning there is no detection of plaque. Nine patients had a "good" plaque index and eight were "reasonable." Only 5 patients received a "bad" plaque index. Twenty-three patients showed healthy mucosal disease, while seventeen patients reported gingivitis: mild (n = 12), moderate (n = 4), severe (n = 1).

Fourteen patients were recession-free at the time of the study (Fig. 3). Recessions were seen in twenty-six patients and a total of 70 regions were affected. Fourteen patients remained recession-free after surgery (see Figure 3). Recessions were mainly in the region of post 6-7 (21.43%) and post 2-3 (18.57%). Table 1 gives an overview of each of the observed recessions and their locations. Almost no recessions (n = 4) were noted on the palatal side. Table 2 provides an overview of the complete analysis including p-values and OR for each risk factor. Only a thin biotype and the presence of gingivitis have been shown to be risk factors for developing recessions (p-value < 0.05).

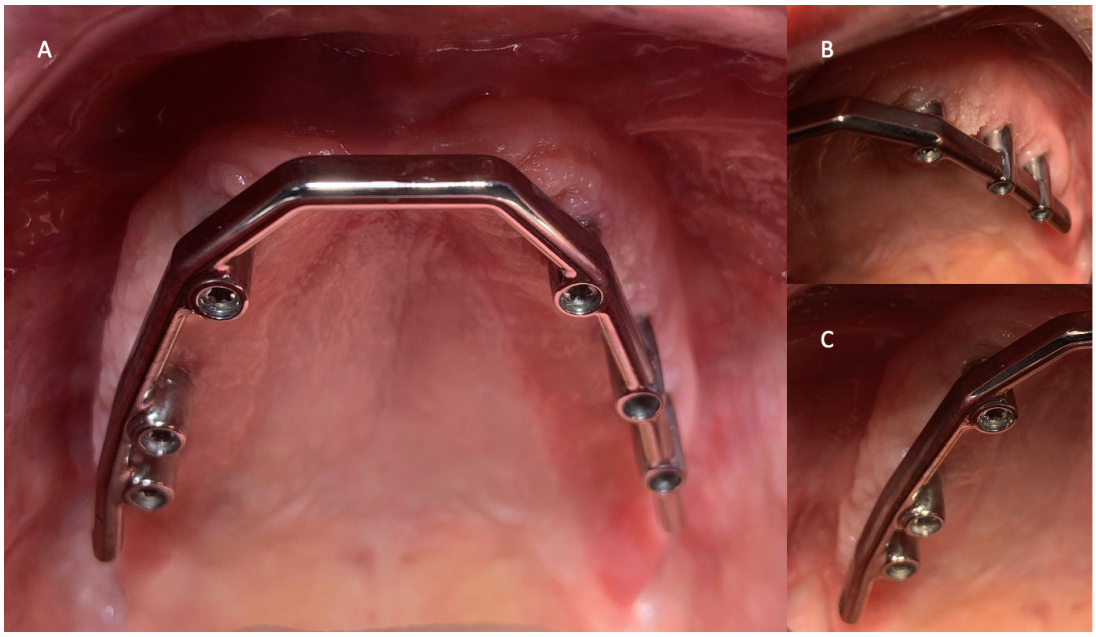

Figure 3. The reaction of soft tissue 4 years after surgery shows a stable situation without recessions. All posts are surrounded by keratinized tissue and a solid interface was found between soft tissue and the transmucosal posts.

A. Upper occlusal view with screw-retained bridge in situ

B. Left side view with screw-retained bridge in situ

C. Right side view with screw-retained bridge in situ

Table 1. Location of recessions

Location of the recession	Buccal	Percentage (%)	Palatal	Percentage (%)
Distal post 2	3	4.29	1	1.43
Post 2-3	13	18.57	0	0.00
Post 3-4	12	17.14	0	0.00
Post 4-5	5	7.14	0	0.00
Post 5-6	10	14.29	0	0.00
Post 6-7	15	21.43	2	2.86
Distal post 7	8	11.43	1	1.43

Recessions were seen in twenty-six patients and a total of 70 regions were affected. Mainly recessions were found buccally in the mid- lateral regions: post 6-7 and post 2-3. Almost no palatal recessions were observed (5.17% of recessions).

Table 2. Static analysis of risk factors

	All patients (n = 40)	No recession (n = 14)	Recession (n = 26)	P-value	OR
Age (median; in years)	61.5	64 (62-69)	61 (59-63)	0.22	0.90 (0.83-1.03)
Gender • Male • Female	 15 (38%) 25 (62%)	 4 (29%) 10 (71%)	 11 (42%) 15 (58%)	 0.39	 1 (ref) 0.55 (0.14-2.20)
ASA • I • II • III	 21 (53%) 18 (45%) 1 (2%)	 7 (50%) 7 (50%) 0 (50%)	 14 (54%) 11 (42%) 1 (4%)	 0.82	 1 (ref) 0,86 (0,23-3,15)
Smoking	10 (25%)	1 (7%)	9 (35%)	0.08	6.88 (0.77-61.4)
Alcohol	17 (43%)	6 (43%)	11 (42%)	0.97	0.98 (0.26-3.64)
Ostectomy	7 (17%)	1 (15%)	6 (85%)	0.23	0.31 (0.04-2.10)
Diabetes	7 (18%)	2 (14%)	5 (19%)	0.70	1.43 (0.24-8.52)
Cardiovascular diseases	10 (25%)	5 (36%)	5 (19%)	0.23	0.43 (0.10-1.85)
Periodontitis	4 (10%)	3 (21%)	1 (4%)	0.11	0.15 (0.01-1.57)
Prothesis • Fix • Bar-retained	 20 (50%) 20 (50%)	 6 (43%) 8 (57%)	 14 (54%) 12 (46%)	0.51	 1.55 (0.42-5.76) 1 (ref)
mPI • Poor • Fair • Good • Excellent	 5 (12.5%) 8 (20%) 9 (22.5%) 18 (45%)	 1 (7%) 3 (21%) 4 (29%) 6 (43%)	 4 (15%) 8 (31%) 4 (15%) 10 (39 %)	0.54	 2.14 (0.56-9.5) ** 1 (ref)
Phenotype • Thin • Thick	 20 (50%) 20 (50%)	 1(7%) 13 (93%)	 19 (73%) 7 (27%)	 **<0.001**	 1 (ref) 0.03 (0.01-0.26)
GI • None • Mild • Moderate • Severe	 23 (58%) 12 (30%) 4 (10%) 1 (2%)	 13 (93%) 0 (0%) 1 (7%) 0 (0%)	 10 (38%) 12 (46%) 3 (12%) 1 (4%)	 **0.006**	 1 (ref) 20.8 (3.4-408) ***

**There were no cases of liver disease, bisphosphonate therapy or radiotherapy*

*** Poor and Fair combined and compared to Good*

Mild, moderate, and severe combined and compared to none

GI: Gingival index; mPI: Modified plaque index; OR: Odds ratio; The results in bold differ significantly between the groups. Only a thin biotype and mucositis can be indicated as a risk factor (p-value < 0.05). Smokers had a nearly seven times (Odds ratio 6.88) risk of developing a recession.

Twelve patients reported after surgery with a postoperative inflammation (i.e., swelling, obvious redness, pain...). All were initially treated with oral antibiotics. Surgical abscess drainage, exploration and/or mechanical debridement was performed in six of these patients, due to persistent infection (Fig. 4). One post had to be removed from three patients each due to uncontrollable infection after abscess drainage/exploration and multiple antibiotic therapies. The stability of the AMSJI or the prosthetic restoration was not affected by the procedure.

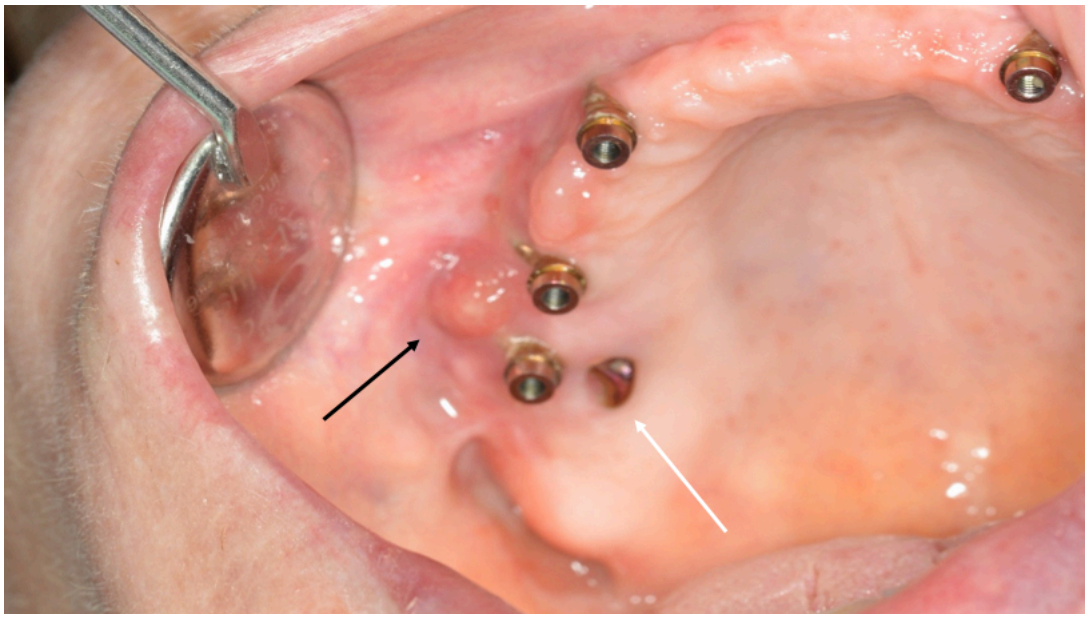

Figure 4. Black arrow: Localized abscess was drained, culture was taken, and appropriate antibiotics were given as treatment.
White arrow: Palatal recession due to postoperative localized avascular necrosis at post 2-3

Discussion

Implant-prosthetic treatment of a severely resorbed jaw remains a challenge. The use of standard dimension endosseous implants often requires the preliminary use of autologous bone regeneration techniques. representing the "gold standard". However, multiple invasive these procedures involve risks such as infection, donor site morbidity pain, and graft loss, resulting in increased time and cost of treatment. Alternatives such as narrow, short, or tilted implants, or pterygoid, pterygomaxillary, and zygomatic fixtures have been proposed (15-16). However, these still require a minimum amount of basal bone or are surgically demanding. Patients who have previously experienced reconstruction loss often refuse to repeat treatment with these techniques

and accept their edentulous fate. Intractable sinusitis and iatrogenic bone loss have often created an even less favorable situation for further rehabilitation with any endosseous implant solution.

Augmentation procedures and extra-maxillary zygomatic implants can be prevented by using a patient-specific SI. AMSJI® has proven its worth in the past with high patient-related outcome measures and improved impact on oral health (17). Its first mainstay is the "primum non nocere" principle. AMSJI® can be dismantled without leaving any bony damage. The osseointegrative capacity of titanium SIs has been described and the results are promising (18,19). However, the long-term stability of a dental implant is not based solely on its effect on hard tissue. As is the case with conventional dental implant-borne rehabilitation protocols, survival may also depend on healthy surrounding soft tissues. An area of attached keratinized gingiva around the implant shoulder is recommended for endosseous implants because it provides a biological seal (20). The lack of the so-called connective tissue barrier around dental implants is believed to improve access to pathogenic bacteria, resulting in peri-implantitis and ultimately failure of the endosseous implant. Soft tissue recessions are commonly found in modern subperiosteal implants, i.e., Korn et al. experienced partial exposure of the underlying framework in 47.36% of patients (21).

Our study indicated that biotype plays an important role and can be indicated as a statistically significant risk factor ($p < 0.001$). This is consistent with several other studies indicating that a thin periodontal phenotype can predispose soft tissue recessions (22,23) and that thin buccal peri-implant soft tissues are associated with an increased risk of mucosal recession (24). Therefore, the determination of the biotype is an important moment in the preoperative evaluation of the patient. If a patient presents with a thin biotype, surgery using soft tissue flaps (free- or pedicled) can be used for biotype conversion. Lin et al. confirmed the efficacy of soft tissue grafting and found that about 1 mm gain from tissue thickness can be expected (24). Korn et al. did not rely on connective tissue grafts for biotype conversions but used gingival and palatal advancement flaps to prevent recession and ensure complete soft tissue implant coverage (21). In zygomatic implant surgery, when implants are placed with an additional sinus trajectory, the use of adipose tissue from the buccal fat pad is suggested to cover the implant surface (25). Alloplastic products such as collagen

matrices have also been used to thicken soft tissue without the need for additional intervention. These materials are imposed between the primary structure and the gingival flap at the time of implant placement, as an all-in-one intervention.

Smoking is a well-documented risk factor for the development of periodontitis (26). Despite the normal appearance of (non-)keratinized mucosa in smokers, smoking promotes epithelial changes like the early stages of dysplasia (27). As a result, a greater epithelial thickness was observed in smokers that can be mistaken for a thick biotype and therefore a protective factor. (28) However, several studies indicate that the cigarette toxins have a detrimental effect on healthy physiological processes and especially disrupt angiogenesis, resulting in a decreasing recovery of damaged soft tissues. (28-29). Impaired wound healing may be one reason why recessions were often seen in smokers after AMSJI installation. This study showed that 90% of smokers (n=9) had recessions. Although smoking was a non-significant risk factor in our study, a nearly sevenfold (OR 6.88) higher risk of developing a recession was seen in smokers. Low numbers may explain this absence of difference.

Mucositis (mild – moderate – severe) can also be charged as a risk factor for the development of recessions. SI have the advantages over classic endosseous implants that the area of mucosal penetration is remote from the internal fixation of the implant framework, as is the case with zygomatic implants. For this reason, the inflammatory state of the (non-)keratinized tissue remains local and does not so easily affect the bone-like fixation points. This may explain why several patients present with localized inflammation, but only one patient had increased mobility of the subperiosteal frame. Still, safety measures should be taken to minimize bacterial invasion and/or colonization of the SI. Meta-analyses report a statistically significantly lower number of dental implant failure when preoperative prophylactic antibiotics are administered (30). After installation of the SI, regular visits to the dentist and/or dental hygienist for monitoring and cleaning the transmucosal posts, suprastructure and prosthesis are also recommended. Should peri-implant gingivitis occur, professional mechanical debridement (supra- and subgingival) with temporary removal of the suprastructure is the treatment of choice because it significantly reduces bacterial levels (31). Using an oral irrigator with 0.06% aqueous chlorhexidine solution reduces peri-implant gingivitis over a 3-month period (32).

To further mitigate the recession for SI, an incision guide could be used. In the past, a mid-crestal incision was performed for exposure of the alveolar process and insertion of the SI.

During suturing, compression of the (non-)keratinized mucosa occurs because the sutures lie perpendicular to the implant. This traction could predispose to the development of recessions and exposure of the framework. With AMSJI, the current version of the guide shows the position where the posts will be located. In this way, the surgeon can decide where to trace the incision line of the flaps, which should be attached to the posts themselves with mattress stitches. A beveled palatally shifted incision line will make it possible to move some keratinized mucosal tissue buccally, increasing its thickness at this level (Fig. 5 and Fig. 6). This apically positioned partial thickness flap will also increase buccal keratinized width (distance from posts to mucogingival border), which helps proper hygiene at the buccal side of the posts. A "certain" amount of peri-implant keratinized tissue seems important to maintain peri-implant bone (33). But can its importance be extrapolated to AMSJI®? Free gingival grafting before endosseous implant placement is indeed still in discussion (34-36).

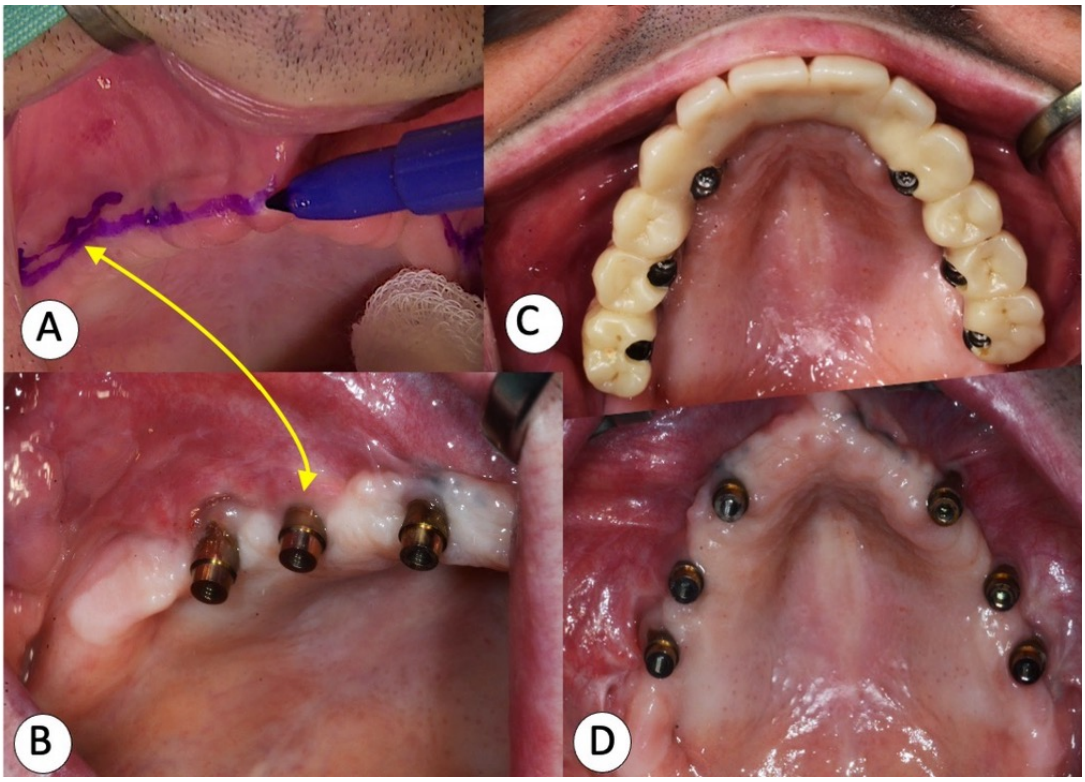

Figure 5. Intra- and 2.5-year postoperative intraoral photos of the implant-soft tissue relationship, showing healthy conditions. The crest incision anno 2020 is more palatal to the top of the top, avoiding a segment of non-keratinized mucosa buccally to a post (yellow arrow).

A: left lateral view with incision marks

B: left lateral view, 2.5 years postoperative

C: upper occlusal display with screw-resistant hybrid bridge, 2.5 years postoperatively

D: upper occlusal view without prosthesis, 2.5 years postoperatively

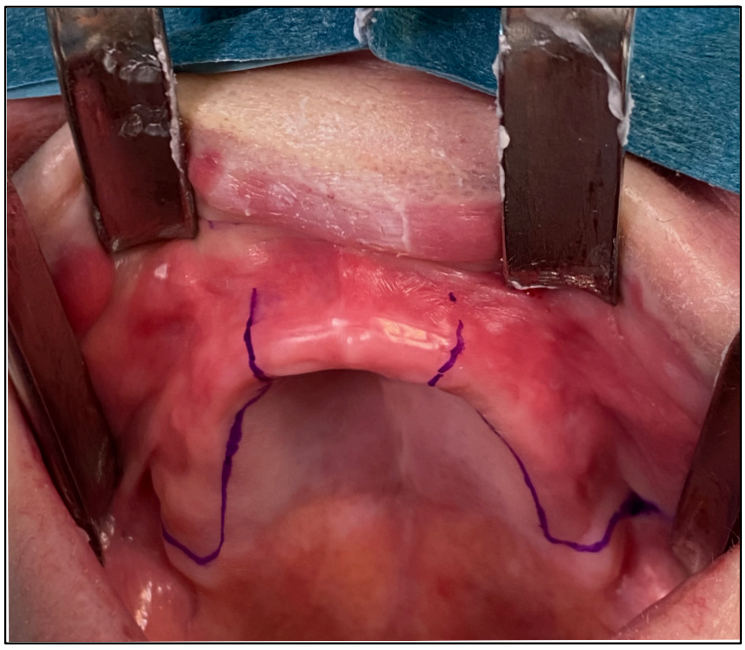

Figure 6. Incision for the exposure of the alveolar process and implantation of the SI is more palatally shifted which will make it possible to move some keratinized mucosal tissue buccally, increasing its thickness at this level and assuring full coverage of the framework

Conclusion

In this study, 40 patients were evaluated after a mean follow-up time of 917 days (SD ± 306.89 days) after maxillary rehabilitation with bilateral AMSJI installation®. Twenty-six patients presented with a recession in one or more of the seven regions. Several risk drivers were evaluated. The collapse of soft tissue around the AMSJI that led to partial exposure of the arms was correlated with the presence of mucositis and a thin biotype ($p < 0.05$). No other risk factors could be indicated, but smoking leads to an almost sevenfold chance of developing a recession ($p = 0.08$). The long-term consequences of recessions in patients with SI have yet to be addressed. Prevention of recessions by apically shifted partial thickness flaps or free grafts of keratinized mucosa is subject for future research.

Conflicting interests: Maurice Mommaerts states that he is an innovation consultant and founder of CADskills BV. All other authors report no conflict of interest.

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Ethical approval: All procedures in studies with human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and according to the guidelines of the 1964 Declaration of Helsinki. The approval of the ethics committee by the institutional review committee of the "Committee on Medical Ethics" (O.G. 016) was granted (protocol code 143201939806). All patients gave written informed consent.

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Chapter VI: How surface coatings on titanium implants affect keratinized tissue: A systematic review

Van den Borre CE, Zigterman BGR, Mommaerts MY, Braem A. How surface coatings on titanium implants affect keratinized tissue: A systematic review. J Biomed Mater Res B Appl Biomater. 2022 Jul;110(7):1713-1723. doi: 10.1002/jbm.b.35025. Epub 2022 Feb 1.

Abstract

Apart from osseointegration, the stability and long-term survival of percutaneous titanium implants is also strongly dependent on a qualitative soft-tissue integration in the transcutaneous region. A firm connective tissue seal is needed to minimize soft-tissue dehiscence and epithelial downgrowth. It is well-known that the implant surface plays a key role in controlling the biological response of the surrounding keratinized tissue and several coating systems have been suggested to enhance the soft-tissue cell interactions. Although some promising results have been obtained *in vitro*, their clinical significance can be debated. Therefore, the purpose of this systematic review is to gain more insight into the effect of such coatings on the interface formed with keratinized soft tissue *in vivo.* A comprehensive search was undertaken in March 2021. Relevant electronic databases were consulted to identify appropriate studies using a set of search strings. In total, 12 out of 4971 publications were included in this review. The reported coating systems were assigned to several subgroups according to their characteristics: metallic, ceramic and composite.

Notwithstanding the differences in study characteristics (animal model, implantation period, reported outcomes), it was noticed that several coatings improve the soft-tissue integration as compared to pristine titanium. Porous titanium coatings having only limited pore sizes (<250 μm) do not support dermal fibroblast tissue attachment. Yet, larger pores (>700 μm) allow extensive vascularized soft-tissue infiltration, thereby supporting cell attachment. Nanostructured ceramic coatings are found to reduce the inflammatory response in favour of the formation of cell adhesive structures, i.e., hemidesmosomes. Biomolecule coatings seem of particular interest to stimulate the soft-tissue behaviour provided that a durable fixation to the implant surface can be ensured. In this respect, fibroblast growth factor-2 entrapped in a biomimetic apatite coating instigates a close to natural soft-tissue attachment with epidermal collagen fibres attaching almost perpendicular to the implant surface. However, several studies had limitations with respect to coating characterization and detailed soft-tissue analysis, small sample size and short implantation periods. To date, robust and long-term *in vivo* studies are still lacking. Further investigation is required before a clear consensus on the optimal coating system allowing enhancing the soft-tissue seal around percutaneous titanium implants can be reached.

Keywords: titanium, coating, soft-tissue integration, transcutaneous implant, keratinized tissue, implant

Introduction

Titanium (Ti) implants are used in many different medical specialties, such as oro-cranio-maxillo-facial surgery, dentistry, orthopaedic surgery, and neurosurgery. They are used to replace bone tissue, stabilize bone segments, or anchor prostheses in load-bearing and non-load-bearing conditions. To guarantee implant stability, a secure and lifelong anchoring in the native surrounding bone, i.e., osseointegration, is required. This is defined as the direct structural and functional connection between living bone and the surface of a load-bearing implant without an intervening soft-tissue layer[1]. For applications in which the Ti-implant is penetrating the skin to be connected to an extracorporeal part (e.g., in bone anchored hearing implants, dental implants, maxillofacial and orthopaedic devices), not only osseointegration is needed, also a firm interface between implant and surrounding soft tissue is an important prerequisite for survival[2-4]. The formation of a long-standing biological barrier, with direct attachment of keratinized tissue to the implant surface, is necessary for long-term implant success and viability[2-5].

Over the years, the concept of osseointegration of Ti implants in the host bone has already been extensively researched and described[1,6,7]. The soft tissue integration of Ti, however, has been far less studied, although several authors have highlighted the importance of a firm soft-tissue seal to optimize implant survival[2,7,8]. Ideally, the epithelial-implant interface is characterized by a thin soft-tissue capsule including only a low number of inflammatory cells and fibroblasts. Furthermore, the collagen fibre orientation should be perpendicular or oblique to the implant surface[3, 9, 10] otherwise, no direct soft tissue-implant adherence is achieved[11].

The implant surface plays a critical role in achieving a desirable cell and subsequent tissue response around implants. It is well accepted that the excellent biocompatibility of Ti and its alloys, owing to the presence of a protective oxide layer on the surface which remains highly stable even in the hostile biological environment, is at the basis of a direct bone apposition favouring osseointegration[12]. Yet, achieving a permanent direct attachment of soft tissue seems more challenging[8]. Animal experiments have revealed a barrier epithelium in direct contact with the TiO_2 surface through hemidesmosomes. But collagen fibre bundles remain parallel to the implant surface and

not perpendicular. Hereby a true chemical and therefore mechanical bonding to the titanium surface is not established[13].

Surface modification of Ti to fine-tune the surface physicochemical properties has been suggested to augment soft tissue integration[5]. However, conventional surface modification techniques such as bead blasting, etching or anodization, alter the original surface of the substrate. Coatings do not have this effect. Rather, coating enables the complete coverage of the pristine metal surface with a biologically active material that encourages the host cell interaction, without modifying the original surface[14]. Several coatings, mainly materials mimicking the components of living tissue, have been investigated for their potential to activate epithelial and/or fibroblast functions, such as inorganic CaP based coatings or biological coatings of extracellular matrix (ECM) components or growth factors[5]. Yet, many of these studies only involve *in vitro* research, which sometimes varying outcomes. Moreover, the clinical significance of *in vitro* results is controversial because methodologies often do not consider the complexity of the *in vivo* situation.

With this systematic review focused on *in vivo* evaluation, we aim to gain more insight into the effect of coatings on the Ti implant-keratinized tissue interface characteristics with the purpose of identifying those coatings that significantly improve the peri-implant seal *in vivo* and therefore are most promising for further clinical investigation.

Methods

Eligibility criteria

Studies eligible for this review were: original research papers, case reports, (non-) randomized control trials and prospective and retrospective studies/case series, systematic reviews, and meta-analyses. Technical notes, editorials, letters to the editor, opinions, or commentaries, which did not present original data were withheld. Only studies regarding the effect of coated Ti implants on the keratinized tissue seal were included. Studies solely researching the interface between Ti and bone were excluded. If studies reported results concerning the effect on soft tissue and osseointegration, only the keratinized results were accounted for. Only *in vivo* research was considered, this included animal studies as well as studies involving human subjects. *In vitro* research on soft tissue healing and fibrosis was not considered, as these studies often lack consensus. Furthermore, research methods applied for *in vivo* and *in vitro* studies differ too much, thereby hindering a reliable comparison of the results. No restrictions with respect to the publication date were imposed. Only the English, German, French and Dutch literature was checked.

Information sources and search strategy

The systematic literature search was performed using the following electronic databases: PubMed Central (www.ncbi.nlm.nih.gov/pubmed), Cochrane Library (www.cochranelibrary.com), Embase (www.embase.com), and Web of Science (https://www.webofknowledge.com). Next, the following trial registers were screened to include the most accurate and up-to-date research: clinicaltrials.gov and trialregister.nl. Finally, to extend the search, reference lists of the relevant studies were screened for relevant articles and filtering cited articles. A detailed overview of the Boolean searches together with the search results is given in table 1 and figure 1.

Table 1: Overview of the detailed Boolean search, i.e., a database-appropriate syntax in combination with the selected search terms, and the search result for the consulted databases

Database	Boolean search	Search result
PubMed Central	((((((((((((((((((((((((((titanium[MeSH Terms]) AND coating) OR organic) OR ameloblastin) OR laminin) OR glycosaminoglycans[MeSH Terms]) OR extracellular matrix proteins[MeSH Terms]) OR growth factors[MeSH Terms]) OR DNA) OR biphosphonate) OR antibiotics[MeSH Terms]) OR antimicrobial agent[MeSH Terms]) OR biopolymer[MeSH Terms]) OR inorganic) OR calcium phosphate) OR titanium dioxide) OR nitride) OR metals[MeSH Terms]) OR carbon) OR bioactive glass) OR bioactive ceramics) OR diamond) OR silk) OR bioceramics) OR silica) OR methicone) OR triethoxysilane) AND keratinized tissue)) NOT osseointegration	4235
Embase	(Titanium AND coating AND keratinized OR keratinised) NOT ('osseointegration'/exp OR osseointegration)	270
Cochrane Library	"titanium" in All Text AND "coating" in All Text AND ("keratinised" in All Text OR keratinized in All Text) NOT "osseointegration" in All Text	52
Web of Science	ALL FIELDS: (titanium) AND ALL FIELDS: (coating) AND ALL FIELDS: (keratinized) NOT ALL FIELDS: (osseointegration)	290
www.clinicaltrials.gov	Titanium AND coating	93
www.trialregister.nl	Titanium	31

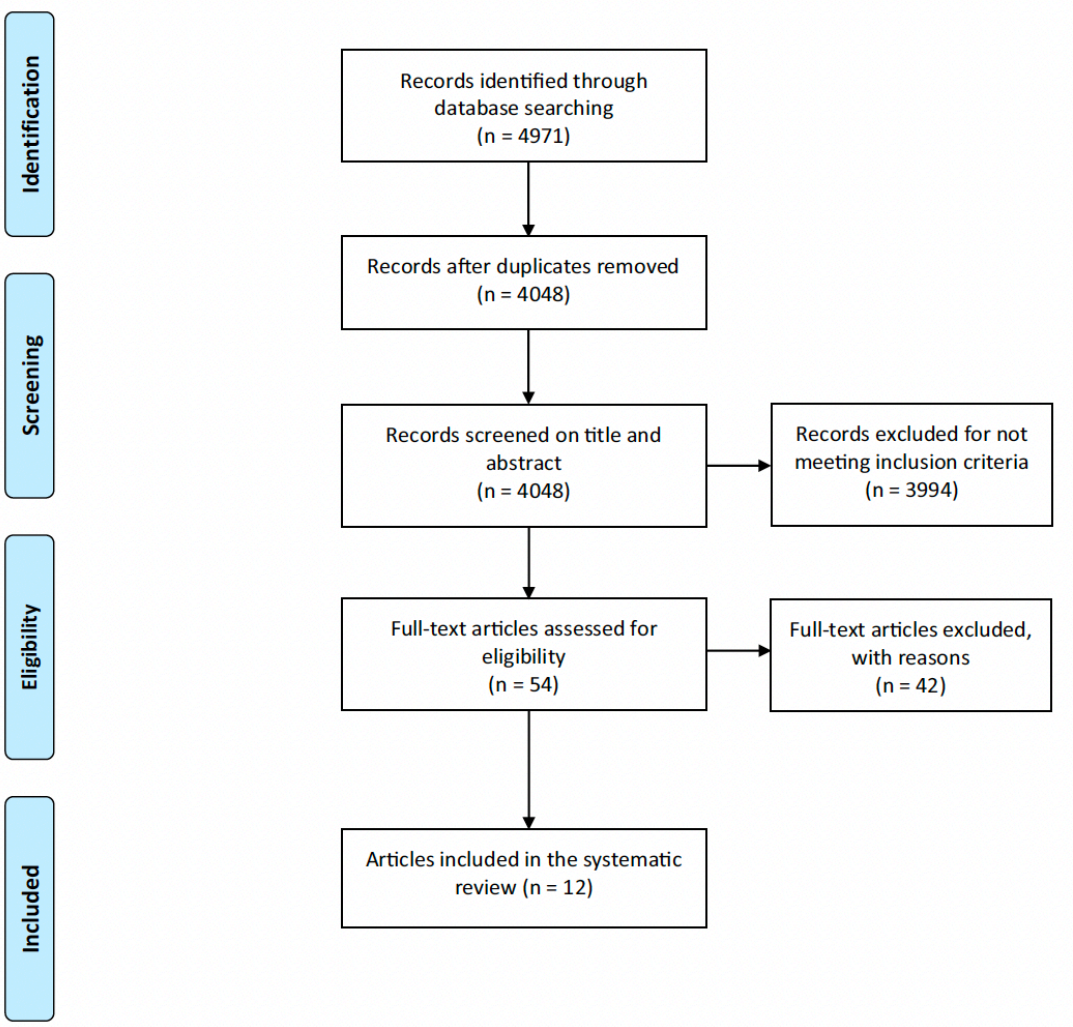

Figure 1: Flowchart with a detailed overview of the search strategy and study selection procedure

Study records

The selection process (screening, eligibility and data extraction) was carried out by two independent researchers (CVDB and BZ). Articles were included through title and abstract screening. If eligible, the full text was analysed and assessed for inclusion. All articles eligible for the systematic review were stored electronically in a full-text version.

Risk of bias in individual studies

An assessment of internal validity, performance, selection, and other types of bias for individual human and animal studies was performed using the OHAT Risk of Bias Rating Tool for Human and Animal Studies. The analysis was done at study level and was carried out by two independent reviewers (CVDB & BZ)

Results

Study selection

The search yielded a total of 4971 articles, a detailed overview of the search results per database is shown in Table 1. After initial screening of title and abstract, 54 records were found. The full-text articles were further assessed for eligibility and a total of 12 studies could be included in this systematic review. The overall quality of the studies under review was assessed using the OHAT Risk of Bias Rating Tool for Human and Animal Studies. Results deviated but were acceptable as shown in Table 2.

Table 2: To assess the risk of bias in the included studies, the OHAT risk of bias framework was used.

Author (year)	Selection bias	Confounding bias	Performance bias	Attrition bias	Detection bias	Selective reporting bias
Pendegrass (2006)		+	-	+	++	+
Glauser (2006)		+	-	+	+	+
Welander (2007)	-		-	+	+	+
Rossi (2008)		++	-	+	+	+
Werner (2009)	+		-	+	+	+
Mutsuzaki (2012)	-	+	+	+	++	+
Bates (2013)	-	-	-	+	+	-
De Wilde (2013)			-	+	+	+
Larsson (2015)	-		-	-	+	+
Høgsbro *(2017)*	-		-	+	-	+
Chimutengwende-Gordon (2017)	-	+	+	+	+	+
Li (2020)	+		+	+	+	+

"++": definitely low risk of bias; "+": probably low risk of bias; "-": probably high risk of bias; "- -" : definitely high risk of bias

Study material

A detailed evaluation and data extraction was performed for the 12 selected studies, the major characteristics are listed in Table 3. The study design varied greatly in terms of animal model and time of exposure. Of the selected studies, 3 involved humans and 9 were animal studies, distributed as follows: rabbits (1), dogs (3), rats (1), sheep (2), goats (1), and mice (1). Exposure time varied between 7 days and 12 months. While the Ti material used for the implant was mostly commercially pure (cp) Ti or a Ti6Al4V alloy, the implant geometry differed between studies going from cylinders or screws to discs. Various coating materials were used on the Ti implants: mainly ceramics (hydroxyapatite (HA), titania (TiO_2), diamond-like carbon (DLC)) or metals (porous Ti (pTi)), but also biomolecules (growth factors) as well as composites (combining organic and/or inorganic materials). Depending on the applied coating technique, the thickness of the coatings varied extensively, ranging from 20 nm to 100 µm. For a comprehensive evaluation, results were compiled into specific subgroups based on the coating material: metallic coatings, ceramic coatings, and composite coatings.

A. Subgroup 1 – Metallic coatings

The formation of a firm interface between a Ti implant surface and the surrounding soft tissue is vital for a long-term implant survival. However, in the absence of a firm soft-tissue seal, epithelial downgrowth can destabilize the interface. The formation of a non-adherent, fibrous tissue layer can occur, which decreases implant survival rates. Implant failures have been reduced by various implant designs and by employing different thin, porous metallic coatings on the bare metal surface. Especially, pTi has been investigated to promote soft tissue ingrowth.

pTi has been described by several papers, mainly to investigate the effect on epithelial/subepithelial downgrowth, but outcomes varied. For example, Pendegrass *et al*. (2006) modified machined Ti6Al4V pins with a plasma sprayed pTi layer (thickness: 70-100 µm; pore size: 30-250 µm), but neither the epithelial downgrowth nor the percentage of subepithelial layer attachment was influenced. On the contrary, Ti particle debris detached from the pTi coating and was observed in the soft tissue

surrounded by lymphocytes which could indicate chronic inflammation (depending on the number of lymphocytes present). With respect to soft-tissue ingrowth, only sporadic areas of close attachment and ingrowth were observed in the sub-epithelium. Alternatively, Werner *et al*. (2009) modified the smooth cp Ti surface at the transmucosal part of ITI implants (Straumann AG, Basel, Switzerland) with a pTi coating obtained by sintering of cp Ti beads using electrical discharges (thickness: ca. 400-600 µm; bead size: 125-160 µm)[15]. A good soft tissue healing without any sign of inflammation was confirmed and implants were well integrated with the surrounding tissues (bone, connective tissue, and epithelium) with cells able to colonize the microporosities of the pTi coating. Similar results were found by Chimutengwende-Gordon *et al*. (2017), who compared transcutaneous pins with laser-sintered pTi (pore size: 700 µm) flanges to pins with drilled Ti flanges[16]. It was found that the pTi coating reduced epithelial downgrowth, but the epithelial attachment was similar for both flange materials. Yet, an increased dermal attachment could be observed for pTi flanges and the median percentage soft tissue fill and median density of fibroblast nuclei within the inner pores of the implant was significantly increased for pTi coated as compared to drilled flanges.

B. Subgroup 2 – Ceramic coatings

Ti and its alloys meet many of the biomechanical requirements for load-bearing implants. Moreover, the stable oxide layer that forms at the surface minimizes metal ion release into the biological environment, which largely explains its biocompatibility. However, the material remains bioinert and therefore does not actively support soft tissue adhesion. Owing to their excellent bioactivity, many research efforts have been devoted to ceramic coatings for various applications in soft tissue regeneration.

An often-considered ceramic coating material is HA obtained by a variety of processing routes. Pendegrass *et al*. (2006) investigated the effect of plasma sprayed HA coatings (thickness: 70 µm; average roughness R_a = 2.4 µm with R_a being the arithmetic average of the absolute values of the profile heights) on the soft-tissue interface around bone anchored transcutaneous Ti6Al4V implants in goats. HA coatings did not seem to significantly reduce epithelial downgrowth or improve epithelial or subepithelial attachment when compared to pristine implant surfaces, yet the authors

attributed this to inaccurate positioning of the HA coatings within the soft tissues. This does not correlate to the results obtained by Larsson *et al*. (2015) who investigated the effect of a plasma sprayed HA coating (thickness: 80 µm) on smooth cp Ti bone anchored hearing implant (BAHI) abutments fixed to Ti implants using a sheep model[17]. Here, it was found that after 4 weeks, epidermal downgrowth and pocket depths were significantly reduced for HA coated abutments, hereby demonstrating improvements in soft-tissue integration regarding the intimate dermal junction. However, in a clinical study including 25 human subjects, H*øgsbro et al*. (2017) evaluated the keratinized tissue-implant interface for plasma sprayed HA coatings (thickness: 80 µm; R_a = 7 µm) on smooth cp Ti BAHI abutments[18]. After a follow-up period of 1 year, it was concluded that the HA coating did not significantly improve the soft-tissue reaction in comparison to smooth Ti abutments. Alternatively, to the relatively rough plasma sprayed coatings, implants featured with a nanostructured HA coating have been investigated as well. A study in humans by De Wilde *et al*. (2013) investigated the soft-tissue response to nano-HA (thickness: 20-30 nm; average roughness S_a = 1 µm with S_a being the arithmetic mean of the absolute values of the surface departures from the mean plane) coated cp Ti dental implants installed in the jawbone[19]. After 8 weeks of implantation, implants were removed and immunologically and histologically evaluated. No significant differences in terms of inflammatory response in the transmucosal regions were found for the nano-HA coated surfaces as compared to uncoated Ti. Different results were observed for nanostructured HA coatings applied by a combination of alkali treatment and subsequent hydrothermal treatment. Li *et al*. (2020) investigated the effect of nanorod HA coatings (thickness: 3 µm; R_a = 0.24 µm) on cp Ti on skin integration for percutaneous rods in a mice model[20]. Whereas a thick fibrous capsule of 400 µm was observed at the soft tissue – implant interface around uncoated cp Ti rods, the capsule thickness decreased to about 100 µm for nanorod HA coated implants. This effect was further improved when silicon was substituted into the nanorod HA coatings (Si-HA), as illustrated by an even more reduced epithelial downgrowth and the absence of a fibrous capsule around the implant, indicating a tighter seal between the surface and the underlying dermis.

TiO_2 is another ceramic that is often investigated as coating material to improve the soft-tissue response to percutaneous implants. For example, Glauser *et al*. (2006)

prepared TiO_2 coatings on cp Ti by means of microarc oxidation which resulted in a characteristic microporous oxidized surface layer[21]. These dental implants were installed in 5 human patients and compared to a machined or acid-etched surface following a transmucosal healing period of 8 weeks. Implants were harvested with a layer of surrounding hard and soft tissue and the histomorphometric characteristics of the peri-implant soft-tissue barrier were investigated. It was observed that TiO_2 modified implants reduced downgrowth of epithelia as compared to machined Ti implants, yet the connective tissue was oriented circumferentially to the implant surface without any perpendicularly oriented collagen fibres directly contacting the implant surface. Bates *et al.* (2013) also prepared TiO_2 coatings by means of microarc oxidation[22]. Six implants were installed in a rat model and harvested after 4 and 8 weeks. At both time points, histological assessment showed connective tissue in intimate contact with the implant surface. After 8 weeks, a greater depth of penetration into the implant grooves was seen when compared to 4 weeks. However, no perpendicular collagen fibres were seen. A layer of adipose tissue was noted adjacent to the fibrous tissue.

Alternatively, also sol-gel derived TiO_2 coatings have been considered to improve the peri-implant tissue response. As such, Rossi *et al*. (2008) evaluated nanoporous TiO_2 thin films (thickness: 380 nm; S_a = 0.26 µm) coated on the smooth cp Ti surface at the transmucosal part of ITI implants (Straumann AG, Basel, Switzerland) in a beagle dog model[23]. Scanning electron microscopy (SEM) evaluation after 8 weeks of implantation showed numerous gingival cells attached to the coated implant surface. In all specimens, keratinized oral epithelium was seen that was continuous with the junctional epithelia facing the implant surface. Furthermore, histological examination showed a mild or absent inflammatory reaction in peri-implant connective tissues around the surface coated implants. In contrast, unmodified surfaces were seen to instigate a capsule-like structure leading to minor cell adhesion as illustrated by a total detachment of the junctional epithelium from the implant surface in 45% of the reported implants. When analysed by transmission electron microscopy, dense plaques of hemidesmosomes were revealed facing the surface-treated implants.

Finally, DLC has been suggested as a coating material exhibiting low surface energy and concomitantly low bacterial adhesion, originally only for external parts of

transcutaneous implants not in contact with the soft tissues to reduce infections. Pendegrass *et al*. (2006) compared DLC-coated sandblasted or grooved Ti6Al4V to uncoated machined Ti6Al4V bone-anchored transcutaneous implants in a goat model for 4 weeks. There were no clinical signs of infection, but DLC coatings did not seem to affect the epithelial downgrowth or epithelial/subepithelial layer attachment.

C. Subgroup 3 – Composite coatings

To further tailor the coating properties to the specific requirements of a targeted application, combinations of two or more materials that form a layered or mixed structure have been proposed. These so-called composite coatings synergistically combine the functionalities of both materials for an improved therapeutic effect which can otherwise not be realized by a traditional coating. Based on the nature of the coating materials, inorganic-inorganic, organic-inorganic and organic-inorganic composite coatings have been identified in the here reviewed *in vivo* studies.

Inorganic-inorganic coatings

One coating type involving multiple inorganic materials that was investigated in several papers was the layered combination of pTi, for an improved ingrowth of soft tissue in the porous layer, with a HA, to improve fibroblast attachment (Pendegrass *et al.*, 2006). In an *in vivo* study in goat tibiae, Pendegrass *et al*. (2006) did not observe differences in soft-tissue morphology around transcutaneous machined Ti6Al4V implants whether or not coated with a plasma sprayed pTi layer (thickness: 70-100 µm; pore size: 30-250 µm) including a plasma sprayed HA top coating (thickness: 70 µm). Downgrowth and epithelial or subepithelial tissue attachment was not significantly different. Here as well, a DLC coating was considered for the external parts, yet a decreased epithelial and subepithelial layer attachment was observed, however, this was not statistically significant. Alternatively, Chimutengwende-Gordon *et al*. (2017) investigated transcutaneous pins with laser-sintered pTi (pore size: 700 µm) flanges with an electrochemically deposited HA topcoating (thickness: 30-76 µm) in an *in vivo* sheep model. Other than the plasma spraying method, which is a line-of-sight process, electrochemical deposition allows to also coat the inner pores of the pTi (thickness: 12-55 µm). Moreover, it is a versatile process enabling incorporation of

substituting ions, such as silver, within the HA (Ag-HA) for antimicrobial activity upon release. Whereas pristine laser-sintered pTi flanges already showed an improvement in comparison with drilled flanges including a plasma sprayed HA top coating (see subgroup 1), inclusion of HA and Ag-HA top coatings on pTi flanges did not further reduce epithelial downgrowth nor was the epithelial or dermal attachment and soft-tissue fill or fibroblast nuclei density in the inner pores further improved.

Organic-inorganic coatings

Organic biomolecule coatings have been of keen interest to improve the implant-soft tissue seal by targeting enhanced adhesion and proliferation of epithelial cells and fibroblasts[5]. Yet, in literature, different methods are used to apply these biomolecules on the implant surface. Methods used to attach biomolecules to the implant surface can typically be classified into three categories, i.e., physical adsorption to the substrate, physical entrapment in an additional coating layer or chemical grafting to the implant substrate through irreversible chemical links[24]. All these categories were also represented in the here reviewed *in vivo* studies.

Firstly, Chimutengwende-Gordon *et al*. (2017) applied fibronectin (Fn), an anchoring protein regulating cell attachment and mobility, through physical adsorption by means of simple immersion on HA or Ag-HA coated pTi flanges (laser-sintered pTi flanges, pore size: 700 µm; electrochemically deposited HA top coating, thickness: 30-76 µm, see above) on transcutaneous pins. These Fn modified HA (HA/Fn and Ag-HA/Fn) surfaces were evaluated in a sheep model for 4 weeks. Epithelial downgrowth and attachment was similar as observed for pTi, pTi+HA and pTi+Ag-HA as well as the soft-tissue fill and density of fibroblast nuclei within the inner pores of the implant. Dermal attachment to Fn modified surfaces, however, was improved in comparison to their unmodified counterparts.

Alternatively, to this simple adsorption method, Welander *et al*. (2007) partially integrated the structural ECM protein collagen type I in an anodically formed oxide layer on a cp Ti implant surface by an electrochemical process[25]. The soft-tissue reaction was evaluated in a beagle dog model for 4 and 8 weeks. It was found that the vertical dimensions of the epithelial and connective tissue components of the soft

tissue/implant interface were similar for collagen-coated implants as compared to cp Ti controls. The epithelial cell attachment was also similar for both conditions. As SEM analysis could not identify the collagen coating anymore after 4 weeks, the authors hypothesize that the coating degraded prematurely. Mutsuzaki et al. (2012) used a similar approach to incorporate fibroblast growth factor-2 (FGF-2), known to facilitate fibroblast proliferation and angiogenesis which promotes cell interaction, viability, and attachment, in a calcium phosphate coating by means of biomimetic deposition[26]. *In vitro* testing confirmed that FGF-2 was released from the coatings for at least 4 days, while retaining its bioactivity. The *in vivo* effect of FGF-2/apatite composite coatings on soft-tissue healing around percutaneous cp Ti screws was evaluated in rabbits. The FGF-2/apatite composite coating seemed to have a beneficial effect on the soft-tissue/implant interface. An interfacial tissue layer of 100 μm in thickness was formed consisting of an inner and outer layer. While the inner cell layer was directly attached to the FGF-2/apatite composite coating and consisted of thin and stretched cells (0.8–1.7 μm thick and 16–33 μm long), the outer layer consisted of Sharpey fibre-like tissue with many blood vessels and collagen fibres inclined at angles from 30 to 40° to the screw surface.

Bates *et al*. (2013) investigated the effect of platelet derived growth factor (PDGF) and enamel matrix derivative (EMD) coatings on the connective tissue attachment to TiUnite (TiO2 coating) implants (Nobel Biocare AB, Göteborg, Sweden) in a rat model. Coatings were applied by physical adsorption by simply immersing the implants in the growth factor solution for 30 s immediately prior to implantation. After 4 weeks of implantation, the connective tissue infiltration around rhPDGF-coated implants was significantly increased in comparison to control and EMD-coated implants. However, after 8 weeks, this difference was no longer significant. Histological assessment showed the presence of an adipose-like layer at the implant surface. No perpendicular attachment of collagen fibres or attachment of fibroblast directly to the implant surface was seen using histological assessment.

Organic-organic coatings

Werner *et al*. (2009) incorporated a laminin-5 derived peptide at the pTi modified abutment surface of ITI implants (Straumann AG, Basel, Switzerland) by means of chemical grafting on an intermediate multi-layered poly(l-lysine) (PLL) / poly(l-glutamic) acid (PGA) polyelectrolyte film (PLL/PGA coating thickness: 60 nm; overall thickness: 80 nm). Laminin-5 is involved in the nucleation and maintenance of hemidesmosomes, the adhesion structures that bind epithelial to the implant surface and are thus involved in the structural scaffolding of epithelial tissues. The authors hypothesized that a peptide including the amino acid sequence representing the integrin-dependent cell-adhesion site on laminin-5 could further improve the cell-adhesion properties of the experimental pTi coating (sintering by electrical discharging, thickness: ca. 400-600 µm; bead size: 125-160 µm; see subgroup 1). Laminin-5-functionalized abutment surfaces were evaluated *in vivo* in a dog model for 6 months and compared with pristine pTi surfaces. Efficient colonization of epithelial cells into the microporosities of the pTi surfaces was observed in both cases. Yet, the study did not include a histological analysis of the soft-tissue organization and remains inconclusive from this perspective.

Table 3a: This table gives more information about the included studies and their major characteristics. If no information was given concerning the characteristics a "-"was placed.

Author (year)	Animal model	Implant geometry	Titanium grade	Coating type	Coating thickness	Coating technique	Time of exposure
Pendegrass (2006)	24 Sarneen goats	Screw (∅ > 4.2 mm x 40 mm) without or with flange (∅ 10 mm)	Ti6Al4V	Screw: HA pTi pTi + HA pTi + DLC pTi + HA + DLC Flange: HA	HA: 70 µm pTi: 70-100 µm DLC: 2-4 µm	HA or pTi: plasma spraying DLC: chemical vapor deposition	4 weeks
Glauser (2006)	5 humans	Screw (M 2.3 mm x 10 mm)	cp Ti	TiO_2 (microporous)	-	Microarc oxidation	8 weeks
Welander (2007)	6 Labrador dogs	Screw (M 3.75 mm x 12.8 mm)	cp Ti	Collagen type I (purified porcine) in TiO_2	40 nm	Entrapment in anodic oxide layer by: 1. anodization in collagen solution 2. immersion in a collagen solution	4 weeks 8 weeks
Rossi (2008)	6 Beagle dogs	Screw (M 4.1 mm x 8 mm)	cp Ti	TiO_2	380 nm (for five layers)	Sol-gel dip-coating (ITI implant)	8 weeks
Werner (2009)	9 Beagle dogs	Screw (M 3.3 mm x 6 mm)	cp Ti	pTi Adhesion peptide (Laminin-5 derived peptide) in PLL/PGA polyelectrolyte film	pTi: ca. 400-600 µm PLL/PGA/laminin-5: 80 nm	pTi: sintering by condensed electrical discharge Laminin-5 derived peptide: immobilization by chemical grafting	6 months
Mutsuzaki (2012)	16 Japanese White rabbits	Screw (M 4.0 mm x 30 mm)	cp Ti	FGF-2−apatite composite layers	0.8 – 1.7 µm	Entrapment in apatite by biomimetic deposition	4 weeks

pTi: porous titanium; HA: hydroxyapatite; C: carbon; cp: commercially pure; Ti: titanium; DLC: diamond like carbon; cp: commercially pure; PLL: poly(l-lysine); PGA: poly(l-glutamic) acid; FGF-2: fibroblast growth factor 2; rhPDGF: recombinant human platelet derived growth factor; EMD: enamel matrix derivative; BAHI: bone anchored hearing implant; Fn: fibronectin; Ag-HA: silver substituted hydroxyapatite; Si-HA: silicon substituted hydroxyapatite.

Table 3b: This table gives more information about the included studies and their major characteristics. If no information was given concerning the characteristics an "-"was placed.

Bates (2013)	12 Dark Agouti rats	Screw (M 3.3 mm x 10 mm)	cp Ti (grade 4)	TiO2 rhPDGF or EMD	-	Microarc oxidation Adsorption by immersion	4 weeks 8 weeks
De Wilde (2013)	13 Humans	Screw (M 1.5 mm x 8 mm)	cp Ti	HA	20 nm	Dip-coating followed by heat treatment	8 weeks
Larsson (2015)	8 sheep	BAHI implant system	cp Ti	HA	80 µm	Plasma spraying	4 weeks
Høgsbro (2017)	25 Humans	BAHI implant system	cp Ti	HA	80 µm	Plasma spraying	1 week up to 12 months
Chimutengwende-Gordon (2017)	6 Sheep	Screw (M 4.2 mm x 45 or 47 mm) with flange (∅ 11 mm x 4.3 or 1 mm)	Ti alloy	pTi pTi + HA pTi + HA/Fn pTi + Ag-HA pTi + Ag-HA/Fn	pTi: - HA: 12-76 µm Ag-HA: 24 – 100 µm Fn: -	pTi: laser-sintering HA or Ag-HA: electrolytic deposition Fn: adsorption by immersion	4 weeks
Li (2020)	Mice (Amount not specified)	Cylinder (Ø 2 mm x 15 mm)	cp Ti	HA Si-HA	3 µm	Alkali-heat treatment followed by hydrothermal treatment	4 weeks

pTi: porous titanium; HA: hydroxyapatite; C: carbon; cp: commercially pure; Ti: titanium; DLC: diamond like carbon; cp: commercially pure; PLL: poly(l-lysine); PGA: poly(l-glutamic) acid; FGF-2: fibroblast growth factor 2; rhPDGF: recombinant human platelet derived growth factor; EMD: enamel matrix derivative; BAHI: bone anchored hearing implant; Fn: fibronectin; Ag-HA: silver substituted hydroxyapatite; Si-HA: silicon substituted hydroxyapatite.

Discussion

Soft-tissue adhesion at the skin/implant interface is crucial for the long-term success of percutaneous implant treatments. However, the formation of a firm bioseal around Ti implants is not easily achieved. Host reactions following implantation of foreign biomaterials lead to acute and chronic inflammation resulting in the formation of granulation tissue. This granulation tissue is separated from the implant by a one- to two-cell layer of monocytes, macrophages, and foreign body giant cells[27]. This layer matures and a fibrous capsule formation is seen as the end-stage healing response[27]. This capsule inhibits a direct adherence of neighbouring soft tissues to the implant surface, which is fundamental to establish a protective barrier against the external environment and harmful microbial invasion and, thus, infection[8].

Epithelial downgrowth is a major factor that destabilizes the soft tissue-implant interface. Downgrowth occurs as a direct result of the so called 'free edge effect'[29]. Due to the absence of neighbouring cells, no signals for proliferation and migration occur and epithelial cells favour to establish layer continuity with the wound edge epithelial cells. Ideally, the surface of epithelium-penetrating implants should impede this apical epithelial migration to ensure implant success. According to Winter *et al*. (1974) the key lies in the dermis[29]. If the dermal cells were to quickly attach to the implant surface, the epithelial cells would not migrate between the dermis and the implant surface. This is exactly what can be observed in percutaneous interfaces around teeth or deer antlers, which can be considered the natural analogues of percutaneous implants. However, one of the major differences compared to Ti implants is the mechanical attachment of the inserting collagen fibres, also called Sharpey's fibres. Rather than engulfing the tooth or antler, these Sharpey's fibres insert perpendicular to the surface of the tooth and provide a firm connective tissue connection. These same angles of implantation must occur to provide the same bioseal on implant level and to prevent apical epithelial recession/downgrowth[4, 8, 26].

Host reactions and healing response are governed by the cellular response to the protein layer formed at the implant surface upon contact with the body fluids. As the composition and conformation of this protein film is determined by the physicochemical surface properties, surface modification of the transcutaneous region of an

implant is an intensively researched strategy to improve the soft-tissue integration[2]. Covering the pristine implant surface with biologically active coatings is a flexible approach allowing introducing the necessary cues to limit foreign body reactions in favour of soft-tissue cell attachment. Many different coatings have been engineered and investigated over the years, but mainly *in vitro* research was conducted[5,8]. This systematic review identified only 12 *in vivo* studies addressing coatings for soft-tissue integration around percutaneous Ti implants. Nevertheless, these covered a wide range of coating strategies, either addressing the surface topography (pTi) or chemistry (ceramics) or introducing truly biologically active organic components (biomolecules) at the implant surface, as well as combined approaches.

Porous structured Ti surfaces are considered for soft-tissue integration as these offer an enlarged specific surface area available for cell attachment and tissue ingrowth[8]. Overall, the here reviewed pTi coatings showed a good soft-tissue reaction, although care should be taken to avoid Ti particle release from the coatings, a complication commonly associated with plasma sprayed Ti coatings and which was found to trigger inflammation[4,30]. The effective establishment of a firm seal at the implant-keratinized tissue interface varied between studies. pTi coatings did not seem to improve soft-tissue integration for straight implants, but a reduced epithelial downgrowth, increased dermal attachment and ingrowth of vascularized soft tissue into the pores was reported for flanged implants with pTi structured flanges[4,31]. Although the implant design was different and a meshed implant collar was previously shown to reduce epithelial downgrowth, differences might also be explained by a discrepancy in pore size in the pTi structures used[32]. It has been previously hypothesized that the anatomical and physiological characteristics associated with soft tissues require a more open pore structure to maintain viable tissue as compared to bone, where 100 µm pore size are considered the lower limit for osseointegration[30]. Indeed, whereas almost no dermal fibroblastic tissue attachment to the implant surface was seen for pore sizes between 30-250 µm, extensive tissue infiltration was observed when the pore size increased to 700 µm[4,16]. This is in correspondence with previous findings by LaBerge *et al*. (1990) who observed fibrous encapsulation for porous coated CoCr implants having pore diameters of 300 µm, while pore diameters of 900 µm became infiltrated with a vascularized soft tissue[33]. This was also confirmed by another study by Chimutengwende-Gordon *et al*. (2018), where it was found that porous Ti implants

having pore sizes of 250 μm did not allow soft-tissue infiltration. It can thus be assumed that the low pore interconnectivity and smaller pores associated with plasma sprayed pTi coatings was not sufficiently promoting cellular infiltration and vascular ingrowth, whereas the fully interconnected open porous structures obtained by laser-sintering, a metal 3D printing technology, facilitated the invasion of blood vessels into the structure which supported early attachment of cells[34].

Altering the surface chemistry of an implant may be considered more effective in controlling cellular behaviour than surface topography and is therefore another valuable approach to fine-tune soft-tissue integration[35]. Inspired by osseointegrative strategies, a frequently considered coating material was HA. Given its close resemblance with the inorganic phase in bone, applications of HA have been mostly related to hard tissue repair. However, several studies have demonstrated its ability to firmly integrate with dermal tissues[9,36]. Yet, when applied as coating, HA seemed to perform poorly *in vivo* with respect to soft-tissue response. Earlier studies, which mainly involved plasma sprayed HA, did not observe a direct soft-tissue contact with the implant surface. However, it should be noted that plasma sprayed HA coatings exhibit a relatively rough surface (R_a = 2 to 7 μm). Alternatively, wet-chemical methods allow introducing a nanotopography as also found in natural tissues. Hydrothermally grown nanorod HA coatings (R_a = 0.24 μm) significantly reduced the inflammatory reaction to pristine Ti, especially when the surface chemistry was further modified by substituting silicon in the HA which accelerated the biosealing[20].

A similar beneficial effect of nanotopography was also observed for TiO_2 coatings. Both microarc oxidized and nanoporous sol-gel derived TiO_2 coatings reduced epithelial downgrowth as compared to pristine Ti[21,23]. But, whereas for microarc oxidized TiO_2 coatings collagen fibres were circumferentially oriented to the implant surface without direct contact, nanoporous sol-gel derived coatings instigated an immediate contact of connective tissue as revealed by the presence of hemidesmosomes. The exact mechanism of soft-tissue attachment, however, remains unclear. It has been shown that the Ti-OH functional groups present on the anatase, and rutile structured titania gel render it a high-energy surface. These TiOH-groups initiate calcium phosphate nucleation, which in turn facilitates adsorption of proteins e.g., fibronectin which mediates the adhesion and spreading of connective tissue cells for a good soft-

tissue integration. Furthermore, the high surface energy presented by these coatings also limit capsule formation which results in a close contact or even direct attachment of soft tissue to the implant surface[23].

Alternatively, instead of fine-tuning the surface topography and chemistry to modulate protein adsorption from the body fluids upon implantation, recent strategies aim to already biofunctionalize the implant surface prior to implantation using bioactive proteins that trigger known cellular responses[24]. A common approach is to include biomolecules at the implant surface that mimic the natural environment of these target cells (cell homing). As such, the adhesive structures through which cells adhere to the implant surface i.e., hemidesmosomes and internal basal lamina, have inspired the use of adhesion related proteins or their functional peptides, such as laminins and fibronectin, but also collagens as structural proteins within the ECM to which cells adhere have been considered[5]. On the other hand, cell-signalling molecules capable of mediating cell behaviour crucial for tissue healing and regeneration, such as growth factors, represent another approach to obtain soft-tissue integration. However, the way these biomolecules are presented to the surrounding media determines the success of such biomolecule coatings[24]. Therefore, coating techniques should not alter the conformation or functionality of the biomolecules. On the other hand, good adhesion of the biomolecules to the implant substrate is also of paramount importance. Biomolecules mimicking the adhesive structures of the ECM are thought to enable a true mechanical attachment of collagen fibres but should in turn also firmly attach to the implant surface to guarantee a good soft-tissue seal. But also, the effect of signalling molecules, which rely on their release from the surface to act on the target cells, can be enhanced if the molecules are retained at the surface over a longer period.

Simple physical adsorption of biomolecules to the implant surface is thought not to affect the biomolecule structure (and hence functionality) much, however, such coatings are only attached to the implant surface through weak interactions (van der Waals forces or electrostatic interactions) and are expected to solubilize upon contact with the body fluids during the early stages of implantation[24]. This can explain why physically adsorbed coating of the anchoring protein Fn onto did not seem to improve soft-tissue attachment to HA-coated pTi transcutaneous pins[16]. Similarly, rhPDGF

coatings on TiUnite implants only showed a beneficial effect on the short-term, as soluble growth factors are prone to rapid enzymatic degradation[22]. For a more durable attachment and activity of the biomolecules, physical entrapment in an inorganic surface coating can be considered[24]. However, the structural ECM protein collagen type I physically entrapped in an anodically grown oxide coating on cp Ti did not improve the soft tissue integration[25]. The authors hypothesized that the collagen degraded prematurely. Promising results, on the other hand, were obtained for FGF-2 which was physically entrapped in biomimetically deposited calcium phosphate coatings[26]. Whereas *in vitro* release testing showed the controlled delivery of FGF-2 for a prolonged period, the *in vivo* experiments confirmed its beneficial effect on soft-tissue attachment. Authors reported Sharpey's fibre-like structures running at 30°-40° degrees inclination to the implant surface. However, it was not discussed how the ends of the collagen fibres inserted in the FGF-2-apatite composite layer. Alternatively, for a long-lasting fixation of the biomolecules to the surface, covalent immobilization through irreversible chemical bonds can be applied[24]. Laminin-5 derived peptide coatings chemically grafted on pTi through an intermediate polyelectrolyte coating as described by Werner *et al*. (2009) showed an intimate implant-soft tissue connection. However, the limited histological analysis performed in this preliminary study did not allow to distinguish differences with the soft-tissue response to pristine pTi.

After considering the results of all reviewed studies, a clear conclusion on the optimal coating system to improve the soft-tissue interface around percutaneous Ti implants and what this would indicate for human studies, cannot be drawn. Several factors hinder a straightforward comparison of the here presented studies. A first restriction is the limited surface characterization performed and inconsistency in reported coating properties. In fact, few papers went into detail about their surface characteristics. A reference was mostly made to earlier publications performed by the same research group; however, this data was mostly limited to coating thickness and average roughness. We have recently made recommendations for a comprehensive surface characterization to correlate with the soft tissue response[37]. Functional coatings tend to be fragile as compared to the high insertion forces applied during implantation and can lose activity upon sterilization or storage.

Another important restriction is that the methodologies for evaluating the soft tissue/implant interface varied significantly between studies, both in approach, profundity and histomorphometric analyses. As indicated above, dermal attachment is a prerequisite to prevent epithelial downgrowth. Unfortunately, not all studies compared the dermal and epidermal connection to coated and pristine implants individually. A comparison of the effect of the different coatings on the soft tissue interface was therefore difficult. Moreover, only a few studies incorporated detailed high-resolution imaging allowing to analyse the orientation of dermal collagen fibres in contact with the implant surface, even though it is believed that a perpendicular insertion of fibres confirms the establishment of a firm bioseal. Another limitation that needs to be addressed is that most studies only report on a small sample size with a variable time of exposure. This could be due to various reasons, amongst others ethical considerations regarding use of animals in *in vivo* experimentation. A small sample size may reduce the statistical power of a study. In very small studies, there exists a possibility of (selection) bias. Therefore, the study quality was assessed by the OHAT risk of bias framework to evaluate risk of bias on study level in human and non-human animal studies. All studies were acceptable according to this assessment. No studies were excluded solely based on sample size, as this can lead to loss of important data.

Conclusion

Overall, 12 publications reporting on the effect of implant coatings on the keratinized soft-tissue interactions have been included in this systematic review. These studies varied significantly in terms of animal model, healing period, and measured outcomes. In addition, often only limited coating characteristics have been reported. Although a direct comparison was not possible, several valuable observations could be highlighted. When compared to the pristine Ti implant surface, metallic pTi coatings improve soft-tissue integration depending on pore interconnectivity and especially pore size. Pore sizes > 250 μm are required to enable dermal fibroblastic tissue attachment, while even larger pore sizes (> 700 μm) enable infiltration of vascularized soft tissue and further support the attachment fiber rich connective tissue to the implant surface. For ceramic coatings, nanotopography, as opposed to a high surface roughness, appeared to be a key feature, and was found to reduce inflammation,

thereby positively triggering the formation of hemidesmosomes. Furthermore, several results indicated that for biomolecule coatings, a prolonged stable presentation of the biomolecule at the implant surface is required to allow a significant biological activity. Growth factors (FGF-2) entrapped in biomimetically grown apatite induced the attachment of collagen fibre-like structures running at 30°- 40° degrees inclination to the implant surface, a near perfect implant-soft tissue interface. Besides some promising results, none of the included studies were able to indicate the formation an implant-soft tissue seal with the same complexity as seen in nature. Therefore, further long-term *in vivo* research is recommended, which should focus on a more comprehensive surface characterization, detailed in-depth soft tissue analyses and their correlation.

Conflict of interest: None

Data availability statement: Data sharing is not applicable to this article as no new data were created or analyzed in this study

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Chapter VII: Titanium surface modifications and their soft-tissue interface on nonkeratinized soft tissues-a systematic review (Review)

Zigterman BGR, Van den Borre C, Braem A, Mommaerts MY. Titanium surface modifications and their soft-tissue interface on nonkeratinized soft tissues-A systematic review (Review). Biointerphases. 2019 Aug 16;14(4):040802. doi: 10.1116/1.5113607.

Abstract

In this systematic review, we explored the surface aspects of various titanium (Ti) or Ti alloy medical implants, examining the interface formed between implant and surrounding non-keratinized soft tissues (periosteum, muscles, tendons, fat, cicatrix, or dura mater). A comprehensive search undertaken in July 2019 used strict keywords in relevant electronic databases to identify relevant studies. Based on our inclusion criteria (restricted to *in vivo* studies), 19 of 651 publications qualified, all pertaining to animal models. The SYRCLE's risk of bias tool for animal studies was applied at study level. Given the broad nature of the reported results and the many different parameters measured, the articles under scrutiny were assigned to five research subgroups according to their surface modification types: mechanical surface modifications, oxidative processes (e.g., acid etching, anodization, micro-arc oxidation), sol-gel derived titania (TiO_2) coatings, biofunctionalized surfaces and a subgroup for other modifications.

The primary outcome being a liquid space at the interface (e.g., seroma formation) was reported in six studies. Machining Ti implants to a roughness between R_a = 0.5 – 1.0 μm was shown to induce soft tissue adhesion. Smoother surfaces, except for acid polished and anodized Ti (R_a = 0.2 μm), prevented soft tissue adhesion. A fibroblast growth factor 2 (FGF-2) apatite composite coating promoted soft tissue attachment via Sharpey-like fibers. In theory, this implant – soft-tissue interface could be near to perfect.

Introduction

The biological and chemical interface between titanium (Ti) and bone has been well characterized already, especially with respect to dental implants.[1] Additionally, numerous studies have addressed the seal between Ti abutments and gingival peri-implant soft tissues.[2] The interface formed between Ti and non-keratinized soft tissues such as periosteum, fat, muscle, tendons, or dura mater has been much less studied. Nevertheless, a thorough characterization of the interface is highly relevant to many surgical fields. In modern craniomaxillofacial surgery, there is an increasing use of Ti alloys, not only for endosseous tooth replacement fixtures, but also for bony substitutes during facial contouring and prosthetic temporomandibular joint surgery, subperiosteal oral rehabilitation, and reconstructive cranial plating. Other Ti-based implants with soft tissue-faced surfaces serve as transcutaneous implants for amputee or laryngotracheal reconstructions, just to name some examples.[3] In fact, reconstructive use of Ti and its alloys is apt to grow even more, given ongoing advancements in Ti 3D printing techniques.[4]

A close contact between implant and soft tissues is regarded as optimal for facial contouring implants as well: a strong soft tissue-implant seal could limit complications such as seroma, hematoma, or abscess formation.[5] The surrounding soft tissue capsule should be thin, with low counts of inflammatory cells and fibroblasts. The collagen fiber orientation should preferably be oblique to the implant surface or randomly oriented; parallel oriented fibers allow for seroma formation to occur between the implant surface and the surrounding capsule.[6] If inordinately strong, however, soft tissue-implant bonding may impose unfavorable adherences, as is sometimes the case in orbital floor reconstructions.[7] For osteosynthesis materials in the facial skeleton, a strong soft tissue seal is regarded as favorable as well for the same reasons as stated above, osteosynthesis material removal is not deemed necessary. From a biological standpoint this means the foreign body reaction of the surrounding tissues should be kept to a minimum by the implanted material. Meaning that the implanted foreign material, in this review Ti, should preferably not be recognized by the body as a foreign material. The surrounding soft tissue should consist of mature type I collagen, in a thin layer: comparable to minimal scar formation.

Various surface properties may influence the response of the non-keratinized soft tissues surrounding the implant/osteosynthesis plate. The surface roughness has been shown to influence soft tissue integration: a certain roughness level could reduce the relative motion between the surrounding soft tissues and the implant surface, allowing direct tissue contact and resulting in a thin soft tissue reaction layer.[8] Sandblasting and acid etching (SLA), which is known to lead to relatively moderate roughness levels, has been shown to stimulate macrophages *in vitro* to secrete the proinflammatory cytokine tumor necrosis factor α (TNF-α) thus increasing the speed of the foreign body reaction.[9] Rough (S_a = 1.8 ± 0.51 μm) Ti6Al4V enhances the secretion of various growth factors such as vascular endothelial growth factor A (VEGF-A), transforming growth factor β1 (TGF-β1) and FGF-2 by human MG63 cells *in vitro*, resulting in a pro-angiogenic and pro-osteogenic environment.[10] On the other hand, for rougher ($R_a \geq 3.3$ μm) surfaces, the surface irregularities easily become permeated by inflammatory tissue, which is regarded as an unfavorable outcome.[11]

Surface wettability and surface energy are proven to be major factors for osseointegration because greater wettability enhances protein adsorption to the implant surface.[12,13] Other research indicated that hydrophilicity alone did not enhance protein adsorption, but combined with a nanostructured surface (Ti sandblasted and acid etched (SLA)) the protein adsorption was significantly enhanced.[14] However, it is important to note that protein adsorption can only be beneficial if specific proteins adsorb to the surface: albumin for example does not promote cell-substrate interaction, but fibronectin does. Hydrophilic implant surfaces enhance bone apposition, but there is not much *in vivo* data on the influence of surface wettability and energy on the soft-tissue implant interface.[15] In cell-substrate adhesion, the cytoskeleton is linked via α and β integrins to implants bearing surface-adsorbed extracellular matrix.[5] Adhesion is then quantifiable by immune labelling of vinculin molecules that link these integrins to the actin cytoskeleton.[5]

Through this systematic review, we explored the ramifications of different surface treatments on various Ti alloy implants, examining interfaces formed between implants and related non-keratinized soft tissue environments. Those elements under investigation included periosteum, muscles, tendons, fat, cicatrix, and dura mater. The primary outcome measure was the presence or absence of a liquid space at the

interface, e.g., a seroma. If a seroma occurs, there is no bonding between the implant and the soft tissues. The purpose of this literature study is to propose Ti surface modifications that may be favorable for further clinical investigation in relationship to their soft tissue behavior, excluding keratinized epithelium and heterotopic bone formation. *In vitro* results were not included in the review, because the *in vitro* research methods differed too much from the *in vivo* research methods for reliable comparison of the results.

Methods

Eligibility criteria

Randomized controlled trials, non-randomized observational studies, and prospective or retrospective cohort studies of humans and animal models were eligible for this review. All studies addressing the bone and Ti (osseointegration) interface and studies of the dental healing abutment-keratinized mucosa interface were excluded, as were all investigations of Ti-based cardiovascular and ocular implants. Osseointegration was explicitly excluded from the Boolean search queries because the purpose of this study is to investigate the effect of different Ti surface modifications on soft tissue-implant interface. A too broad search query may clutter the results. Furthermore, reviews into Ti surface modifications to improve osseointegration have been carried out recently.[16,17]

Only *in vivo* research qualified for this systematic review. If a selected paper combined *in vivo* and *in vitro* studies, the *in vivo* aspect alone was reviewed. English, Dutch, French, and German language articles were all considered.

Information sources and search strategy

Electronic database searches of PubMed and the Cochrane library were conducted, detailing Boolean searches Table 1. The search process was extended by filtering reference lists for relevant articles and filtering cited articles. The following trial registers were screened to potentially include ongoing or near-complete studies: www.trialregister.nl and www.clinicaltrials.gov

Table 1 Boolean searches

Database	Boolean search
PubMed library	(((titanium[MeSH Terms])AND (((((((soft tissue) OR periosteum[MeSH Terms]) OR dura mater[MeSH Terms]) OR muscle) OR adipose tissue[MeSH Terms]) OR subcutaneous fat[MeSH Terms]) OR cicatrix[MeSH Terms])) AND surface
Cochrane library	Titanium NOT osseointegration
www.clinicaltrials.gov	Titanium, soft tissue
www.trialregister.nl	Titanium

Study records

Study prioritization (screening, eligibility, and data extraction) was achieved by two independent reviewers (BZ & CVDB). We downloaded and stored all relevant articles in full-text versions, extracting data for insertion into standard piloting forms. If specific data therein appeared questionable, listed authors were contacted for clarification. For those who failed to clarify or respond, 'unknown' served as the default.

Outcomes and prioritization

Extracted data are itemized in Table 2. Liquid space at the interface was the chosen primary outcome measure. If this measure was unavailable, surrogate outcomes such as fiber orientation, capsular quality and quantity, liquid present at implant-soft tissue interface, or immunohistochemical markers were used.[18]

Risk of bias in individual studies and data synthesis

The risk of bias in individual studies was assessed using SYRCLE's risk of bias tool for animal studies.[19] Such analyses were done at study level by two independent reviewers (BZ & CVDB). Study data were qualitatively and (if possible) quantitatively synthesized, as shown in table summaries of study characteristics and respective results. If quantitative synthesis was not feasible, summaries were provided in text.

Table 2 Items for data extraction

Study characteristics	**Implant characteristics**	**Soft tissue characteristics**	**Results**	**Concluding remarks**
• Year of publication • Title • Authors • Number of subjects	• Shape • Titanium, type and grade • Surface modification(s) • Surface measurements: ○ S_a (µm) ○ S_q (µm) ○ R_a (µm) ○ R_y (µm) ○ R_z (µm) ○ *RMS* ○ P_v (µm) ○ R_t (µm) ○ R_{tm} (µm) ○ S_m (µm) ○ *Contact angle* (°) • Roughness in words	• Animal model • Tissue type • Time of exposure	• Liquid space at interface • Fiber orientation • Description of attachment • Percentage of soft tissue attachment • Bonding strength • Histological capsule description • Thickness of the capsule (mm) • Capsule quality score • Semiquantitative score • Interface score • Cell infiltration • Inflammation/infection • Immunohistochemical: ○ *α-SMA* ○ *PNCA* ○ *Fibronectin* ○ *TNF-α*	Conclusion of the study in a few sentences

S_a = arithmetical mean height, S_q = root mean square height, R_a = arithmetical mean height, R_y = maximum height, R_z = ten-spot average roughness, RMS = root mean square height, P_V = peak-to-valley measurement, R_t = total height of profile, R_{tm} = average of five consecutive values of R_t, S_m = mean spacing of profile irregularities. Capsule quality, semiquantitative and interface scores according to Jansen et al. [18].

Results

The search yielded 566 articles from the PubMed database. Of these, 66 qualified for full-text review. Also, 9 articles contributed by the Cochrane library, and all 75 ongoing trials found in trial registers (www.trialregister.nl, 24; www.clinicaltrials.gov, 51) were excluded, failing to meet our inclusion criteria. The searches were last done on July 1, 2019.

After full-text screening and review of references in full-text articles, we selected 25 studies for more detailed evaluation and data extraction. During this phase, 6 studies were in violation of inclusion criteria and were excluded (see Figure 1).

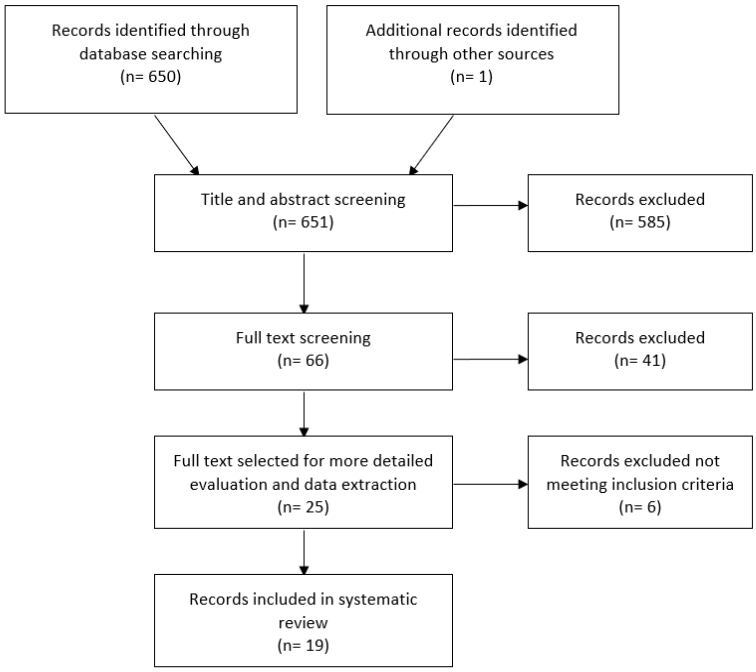

Figure 1 identification, selection and inclusion of articles

There were no available studies involving humans. Only animal models were pursued, distributed as follows: rats (10), rabbits (3), goats (2), sheep (3), and monkeys (1). The nature of Ti also varied, ranging from commercially pure (CP) Ti, grade unknown, to CP grade 2 and grade 4. Ti6Al4V alloy, and Ti15Mo alloy, were used as well. Over twenty different surface treatments (excluding their variations), were tested in the studies selected (duration range: 3 days to 24 weeks). Six studies reported our primary outcome: the presence or absence of a liquid space at the interface.[8,20–24]

The overall quality of studies under review (assessed via SYRCLE's risk of bias tool for animal studies) was fairly good, as shown in Table 3.[25] Because these studies differed greatly in terms of design, animal model, soft tissue beds, and measured outcomes, the results were compiled in specific subgroups. The qualifying studies and their major characteristics are listed in table 4. And their surface modifications are specified in table 5.

Table 3 Risk of bias summary

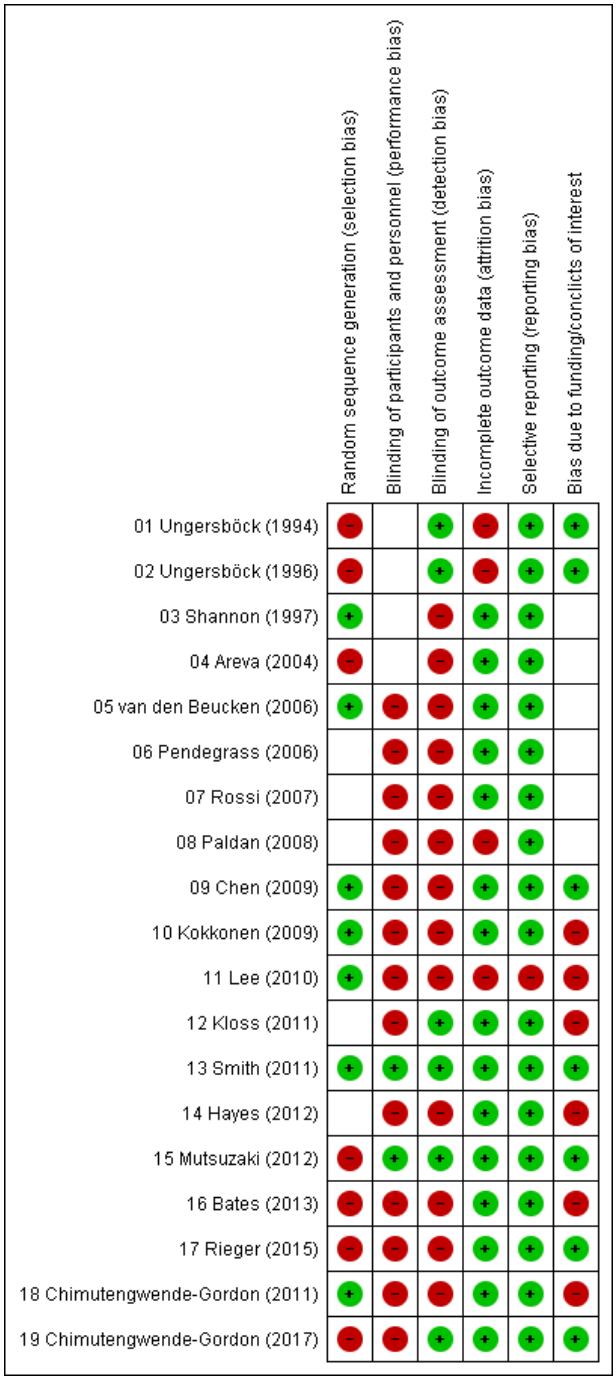

Table 4. Included studies with their major characteristics.

Author (year)	Animal model	Implant type	Titanium type	Surface treatments	Soft tissue	Time of exposure
Ungersböck (1994)	Rabbits	Plates	CP	- Anodized (rough and smooth) - Tumbled - Ground - Sandblasted - Electropolished	Muscles	12 weeks
Ungersböck (1996)	Sheep	Plates	CP	- Anodized (fine, medium and coarse) - Milled - Etched	Muscles	12 weeks
Shannon (1997)	Rats	Cylindrical rods (10*2 mm)	CP grade 4	- As manufactured	Dorsal subcutaneous tissue	6 weeks
Areva (2004)	Rats	Disks and cylindrical rods (7*5 mm)	CP grade 2	- Sol-gel TiO_2 coating - Sol-gel coating + SBF immersion	Dorsal subcutaneous tissue and subperiostal skull area	1 weeks
van den Beucken (2006)	Rats	Cylindrical rods (14*4 mm)	CP	- DNA coating (PDL/DNA) - DNA coating (PAH/DNA)	Dorsal subcutaneous tissue	4 and 12 weeks
Pendegrass (2006)	Goats	Transcutaneous implants (straight and flanged)	Ti6Al4V	- Machine finished - Sandblasted - CAPTAL HA coating - Small grooved - Large grooved - Porous Ti	Epidermis, dermis and subdermal tissue	4 weeks
Rossi (2007)	Rats	Disks	CP grade 2	- Anatase TiO_2 structured sol-gel coating - Rutile TiO_2 structured sol-gel coating	Dorsal subcutaneous tissue	0.43, 1 and 2 weeks
Paldan (2008)	Rats	Cylindrical rods and disks	CP grade 2	- 3 versions of a sol-gel TiO_2 coating	Dorsal subcutaneous tissue	0.43, 1.57, 2, 3, and 12.9 weeks
Chen (2009)	Goats	Transcutaneous flanged implant	Ti6Al4V	- MAO	Epidermis, dermis and subdermal tissue	8 weeks
Kokkonen (2009)	Rats	Cylindrical rods (6*1.8mm)	CP	- MHR-A - MHR-B - AMI	Latissimus dorsi fascia	1 and 3 weeks
Lee (2010)	Macaca Fascicularis	Cylindrical rods (10*3 mm) and plates (8*4*1 mm)	Ti6Al4V	- Osseotite® - HA/BG coating	Muscles and oral submucosa	4, 12 and 24 weeks
Kloss (2011)	Rats	Disks	CP	- H-NCD - O-NCD	Abdominal wall	1 and 4 weeks
Smith (2011)	Rats	Disks (5*2.5mm)	CP	- TiO_2 nanotubes - Gritblasting	Abdominal wall	1 and 6 weeks
Hayes (2012)	Rabbits	Plates (32*5*1mm)	CP Ti-15Mo	- Paste polished - Electropolished - Acid polished	Muscle and periosteum	12 weeks

Mutsuzaki (2012)	Rabbits	Percutaneous implants	Unknown	- Apatite layer - FGF-2/apatite composite layer	Epidermis, dermis and subdermal tissue	4 weeks
Bates (2013)	Rats	Cylindrical rods (10*3.3 mm)	Unknown	- EMD coating - rhPDGF-BB coating	Dorsal subcutaneous tissue	4 and 8 weeks
Rieger (2015)	Rats	Disks (10*2mm)	CP grade 2	- HCl etching - Anodization with and without fetal bovine serum immersion	Dorsal subcutaneous tissue	2 weeks
Chimutengwende-Gordon (2011)	Sheep	Plates (2*1 cm)	Ti6Al4V	- Fibronectin (Fn) - Silanization - Silanization + Fn - Hydroxyapatite - Hydroxyapatite + Fn - Polished	Muscles	4 weeks
Chimutengwende-Gordon (2017)	Sheep	Transcuataneous flanged implants	Unknown	- Porous Ti alloy with hydroxyapatite, HA + fibronectin, HA + Fn and Silver coatings	Epidermis, dermis and subdermal tissue	4 weeks

Table 5. Elucidation of the different surface modifications.

Author (year)	Surface modification
Ungersböck (1994)	- Anodized rough: first blasted, then anodized* - Anodized smooth: first tumbled, then anodized* *Anodizing was performed according to a commercially used treatment for osteosynthesis implants (Stratec Medical)
Ungersböck (1996)	- Anodized fine: anodized according to a commercial standard of anodization at Stratec Medical - Anodized medium: anodized according to a commercial standard of anodization at Synthes-USA - Anodized coarse: anodized according to an experimental procedure at Stratec Medical - Milled: degreased machined surface - Etched: prepared as 'anodized fine' followed by wet blasting and ultrasonic alkaline cleaning, water rinsing and passivating in 20% HNO_3 at 60°C for 30 min
Shannon (1997)	As manufactured: manufactured in accordance with ASTM standard F67.
Areva (2004)	Sol-gel TiO_2 coating: Solution I was prepared by dissolving tetraisopropyl orthotitanate ($Ti((CH_3)_2CHO)_4$ in absolute ethanol. Solution II was prepared by dissolving ethyleneglycol monoethylether ($C_2H_5OCH_2CH_2OH$), deionized water, and fuming HCl (37%) in ethanol. Solution I and II were stirred (> 600 rpm) for 3 min. The coating sol having EtOH:$Ti(OR)_4$, H2O:$Ti(OR)_4$, and HCl:$Ti(OR)_4$ molar ratios of 8.2, 1.0, and 0.018, respectively, was aged at 0°C for 24 h. The coating was applied by dipping the Ti substrates into the sol followed by heat treatment at 500°C for 10 min, and ultrasonically cleaning in acetone for 5 min and in ethanol for 5 min, and finally dried at ambient temperature. This coating cycle was repeated five times to get five layers.
van den Beucken (2006)	The multilayered DNA coating was generated by immersing the substrates in an aqueous solution of either PDL (poly-D-lysine, 0.1 mg/mL) or PAH (poly-(allylamine)hydrochloride, 1 mg/mL) for 30 minutes. After washing in ultra-pure water and drying under pressurized air stream the substrates were alternately immersed in an anionic aqueous poly anionic DNA solution (1mg/mL) and their respective cationic polyelectrolyte solution (PDL or PAH) for 7 minutes each, with intermediate washing and drying. This was continued until a total of five double layers were reached.
Pendegrass (2006)	- Machine finished (MF) - Sandblasted: MF pins blasted with 0.2 mm Al_2O_3 - CAPTAL® HA coating: a 70 µm plasma sprayed coating of CAPTAL® Hydroxy Apatite (Plasma Biotal Limited, Tideswell, UK) was applied to MF pins. - Small and large grooved implants: grooves applied by machining. Small grooved: 0.6 mm depth, 0.5 mm width, large grooved 0.6 mm depth, 1 mm width. - Porous Ti: made by plasma spraying MF pins with a 70 - 100 µm thick, porous Ti layer.
Rossi (2007)	Sol-gel TiO_2 coating prepared as in Arreva (2004). - Anatase structure achieved by furnace heat treatment at 500°C after each coating cycle. - Rutile structure achieved by CO_2 laser treatment with a constant power of 20W after furnace heat treatment.
Paldan (2008)	Sol-gel TiO_2 coating prepared as in Arreva (2004) and Rossi (2007), with different sol aging times: 1h, 24h, and 24h aging time + 4-day immersion in simulated body fluid (SBF).
Chen (2009)	Micro-arc oxidation (MAO) in aqueous electrolyte (0.15 mol calcium acetate monohydrate and 0.02 mol calcium glycerophosphate in de-ionized water, pH adjusted to 11. A 65-kW alternating current with a constant voltage (450V), frequency (500 Hz) a duty of the pulses (12%) was applied to the implants, with each treatment lasting 15 minutes.
Kokkonen (2009)	- MHR-A and MHR-B: Modified hairy regions (MHR) molecules were obtained by treating homogenized apple tissue with commercial pectinolytic enzyme mixtures. Rabidase 600 for MHR-A and Rapidase Rliq+ for MHR-B. The MHR molecules were isolated by centrifuging, ultrafiltration a lyophilation. MHRs were grafted onto an aminated Ti surface by covalently binding the carboxyl groups of the MHRs to the amino groups on the aminated Ti surface. - AMI: an aminated Ti surface was achieved by carbodiimide condensation, in which amino groups were grafted onto Ti via allylamine plasma deposition.

Lee (2010)	- Osseotite® is an acid etching technique developed for improving osseointegration of dental implants. - Hydroyapatite/bioglass (HA/BG) coating was achieved by gritblasting Ti6Al4V plates with Al_2O_3 (60 mesh) followed by radio frequency magnetron sputter deposition of HA granules (sizes 0.5-1.0 mm) and melt-derived bioglass crushed particles (sizes 30-315 µm). The coating was deposited at a discharge power of 100 W for each target and deposition time of 20 h. After deposition, the coated specimens were subjected to an additional heat treatment for 2 h at 650°C.
Kloss (2011)	Nano-crystalline diamond (NCD) coating by a modified hot-filament chemical vapor deposition technique - H-NCD: hydrogen terminated NCD - O-NCD: oxygen terminated NCD, achieved by thermal treatment of the NCD surface at 400°C for 4 h with 21% oxygen. This replaced hydrogen for oxygen-containing groups: carbonyl, ether or hydroxyl groups.
Smith (2011)	- TiO_2 control: grit blasting with a size 22 mesh TiO_2 powders with pore size of 0.8 µm. - TiO_2 nanotubes: electrochemical anodization in a 0.5% HF solution at 20 V for 30 min at room temperature, followed by annealing at 550°C
Hayes (2012)	- CP Ti: machined, paste-, electro- or acid polished. - Ti-16Mo: machined or paste polished. All plates were anodized as the final finishing process.
Mutsuzaki (2012)	- Apatite coating: immersion in a supersaturated calcium phosphate (CaP) solution with a Ca/P molar ratio of 2.0 at neutral pH at 37°C for 48 h - FGF-2/apatite composite coating: immersion in a supersaturated CaP solution with a Ca/P molar ratio of 2.0 supplemented with 4 µg/mL FGF-2 at neutral pH at 37°C for 48 h
Bates (2013)	Implants had a TiUnite® surface, characterized by a moderately rough, thickened oxide layer. - Enamel matrix derivate (EMD) coating: immersion in a 30 mg/mL Emdogain ® solution immediately prior to implantation [26] - Recombinant human Platelet Derived Growth Factor-BB (rhPDGF-BB) coating: immersion in a 0.3 mg/ml rhPDGF-BB solution immediately prior to implantation
Rieger (2015)	- Etching in a 10 M HCl solution for 1 h - Anodization in a 1% HF and 1 M glacial acetic acid solution at 20 V for 20 min followed by annealing at 500°C for 1 h - Both conditions were tested before and after immersion in fetal bovine serum at room temperature for 1 h
Chi-mutengwende-Gordon (2011)	- Adsorbed fibronectin coating: a 12 µl droblet containing 1220 ng fibronectin (Fn) was spread over the surface of the plate. - Silanized + Fn coated plates: silanization was obtained by submerging the plates for 2 hours in acetone containing 10% 3-aminopropyltriethoxysilane (Sigma-Aldrich, Dorset, UK) at 25°C followed by rinsing with acetone and air drying at 37°C. Following this the plates were placed for 2h at 25°C in a 1% glutaraldehyde solution in 0.172M phosphate buffered saline and after rinsing in phosphate buffered saline air dried. The Fn coating was applied as described above. - Control surfaces were polished plates (polishing procedure not further specified), silanized only (without Fn coating), Hydroxyapatite (HA) coating (70 µm thick coating applied using a plasma spraying technique) and HA+Fn coating.
Chi-mutengwende-Gordon (2017)	- Porous Ti was obtained by laser sintering: pore size 700 µm, strut size 300 µm and porosity of 18%. - Hydroxyapatite (HA) coating was applied by electrochemical deposition: immersion of the implant in 0.13M Calcium phosphate monobasic solution. The implant acted as catode, a current density of 58mA/cm^2 was applied for 270 seconds. - HA-fibronectin coating: fibronectin was adsorbed onto the porous flanges by immersing implants into a 3.5 ml solution of phosphate buffered saline containing 2745 ng of fibronectin for 1.5h. - HA-silver (HAAg) coating was applied by electrochemical deposition with 100 mg $AgNO_3$ added per litre of the solution. - HA-silver-fibronectin coating was applied using a combination of the techniques described above.

Subgroup 1 – Mechanical surface modifications

This includes all Ti surface modifications by mechanical means. In most publications, machined or sandblasted surfaces were included as control group.
Ungersböck et al. found that tumbled, handground and Al_2O_3 blasted cp (grade unknown) Ti plates placed on the tibia under the leg muscles in rabbits did not have a liquid space at the interface, and no significant differences in thickness of the capsule were found after 12 weeks of implantation.[20] However, significantly more foreign body giant cells were seen at the peripheries of Al_2O_3 blasted Ti plates (R_a = 1.50 ± 0.24 µm) compared to smooth anodized Ti plates (R_a = 0.33 ± 0.06 µm).[20] In the follow up study by the same research group in sheep, rupturing fibers were found in the capsule around a milled Ti plate (R_a = 0.91 ± 0.1 µm) placed on the tibia under the leg muscles, indicating soft tissue attachment.[8] Shannon et al. compared a machined Ti cylindrical implant with a stainless-steel implant.[27] The Ti implant was of medium-smooth surface (R_a = 0.55 ± 0.16 µm) and showed subjectively good adhesion to soft tissue, achieved by parallel, loosely organized capsular fibers. This thin capsule (45 ± 11 µm) was chiefly composed of type I collagen after just 6 weeks.[27] Subjective adhesion is noted if the authors describe a (more) difficult removal of the implant from the surrounding soft tissues.

Pendegrass et al. studied flanged and straight Ti6Al4V transcutaneous implants in goats.[28] Around all straight implants, epithelial downgrowth was found, around machine finished (R_a = 0.21 µm) and rough sandblasted (R_a = 0.4 µm) implants, the epidermis never contacted the implant surface and terminated within the dermis. Around small and large grooved implants, dense populations of inflammatory cells were found with sporadic subepithelial layer attachment on the peaks of the grooves, not in the troughs. Flanged implants however reduced epithelial downgrowth, and a seal between subepithelial tissue and the implant surface was observed.[28]

Subgroup 2 – Acid etching, anodization, micro-arc oxidation

In this subgroup, all surface modifications aiming to improve the thick TiO_2 layer surrounding the implant by acid etching, anodization, or micro-arc oxidation (MAO) were included.

Rough anodized Ti plates (R_a = 0.75 ± 0.19 µm) seemed to be favorable in terms of a thin connective tissue layer surrounding the implant, without any liquid space in the interface and with low inflammatory cell counts in the rabbit study by Ungersböck et al.[20] In their sheep study, coarse anodized Ti plates (R_a = 0.78 ± 0.1 µm) revealed thinner reaction layers compared to milled Ti plates, but both had rupturing fibers inside the capsule upon lifting the soft tissues, indicating soft tissue attachment.[8] Whereas the fine anodized Ti plates (R_a = 0.44 ± 0.1 µm) had in 2 out of 7 cases a liquid space at the interface and parallelly orientated fibers in their capsule.[8]

MAO of flanged screw transcutaneous Ti6Al4V alloy implants placed in goats legs resulted in sporadic sub-epithelial soft tissue ingrowth with areas of close attachment to the coarse implant surface.[23] The percentages of soft tissue attachment were 90.16 ± 9.96% for the MAO treated group, and 3.62 ± 1.97% in the control group.[23] Soft tissue attachment was quantitatively evaluated by analyzing three sections for each implant and randomly selecting three areas of the implants for measurements under light microscopy.[23]

Osseotite® is a specific mode of acid etching. Osseotite® Ti6Al4V alloy bullets placed in the rectus femoris muscle of macaca fascicularis for 12 and 24 weeks showed a medium thin capsule with parallel organized fibers at both time points.[29] The capsule was easily detached from the implant, but no significant differences in muscle tissue responses between the machined and Osseotite ® surface bullets were noted.[29]

Smith et al. hypothesized that by increasing the TiO_2 surface of Ti disks (Ø 5mm x 2.5 mm) by anodization, the catalytic and semiconductor properties of the TiO_2 nano-tube modified implant would increase the degradation of nitric oxide (NO) species, and thus decrease the inflammatory reaction.[30] Grit blasted and anodized cp Ti im-plants were compared, both with a macroscale roughness of S_a < 1.0 µm, nanoscale roughness parameters were, however, not reported, contact angles were 4° for the TiO_2 nanotube modified surface, 54° for the grit blasted cp Ti.[30] After both 1 and 6 weeks of implantation, the fibrotic capsule surrounding the anodized implant was thinner compared to the grit blasted implants.[30] Significantly lower NO activity was found adjacent to the TiO_2 nanotube modified implant after 1 week, meaning there

was a less extensive foreign body reaction. At six weeks, this difference disappeared, but there was a still a lower concentration of monocytes and macrophages per fibrotic capsule area compared with grit blasted Ti implants. The cell infiltration around TiO_2 nanotube modified implants decreased between 1 and 6 weeks as well.[30]

Hayes et al studied cp Ti (grade unknown) and titanium-molybdenum alloy (Ti-15Mo; ASTM F2066) in different versions: machined, paste polished, electropolished and acid polished.[24] All plates were anodized as the final finishing process. Liquid spaces at the interface were observed for the smooth paste polished cp Ti (R_a = 0.3 µm, contact angle 69°), electropolished cp Ti (R_a = 0.2 µm, contact angle 68°), and paste polished Ti-15Mo (R_a = 0.3 µm, contact angle 72°).[24] However, the smooth acid polished cp Ti surface (R_a = 0.2 µm, contact angle 71°), did not induce a liquid space at the interface, but an attached connective tissue layer was formed. This could also be observed for the standard micro-rough surfaces of cp Ti (R_a = 0.9 µm, contact angle 70°) and Ti-15Mo (R_a = 1 µm, contact angle 75°). Smooth surfaces manufactured by paste- or electropolishing followed by anodization seem to prevent soft tissue adhesion in the legs of rabbits.[24]

Rieger et al. found that acid etching of cp grade 2 Ti resulted in more tissue formation around the implants, with more cell infiltration compared to a machined or anodized surface, surface roughness was comparable around R_a = 0.02 µm in the different surface versions.[31] Submerging the implants in fetal bovine serum for 1 h ameliorated these results for all surfaces, but mostly for the acid etched implant.[31]

Subgroup 3 – Sol-gel derived TiO_2 coatings

This subgroup, includes different versions of sol-gel derived titania (TiO_2) coatings, researched by the same research group based in Turku, Finland.[21,22,32] In their first animal study, short term (up to 12 days) soft tissue attachment was proven with occasionally attached fibers observed by scanning electron microscopy, whereas a clear gap between the soft tissues and the non-coated control implants was noted.[32] In their follow up study, the sol-gel derived TiO_2 coating was heat treated into rutile and anatase crystal structures.[21] After three weeks of implantation this resulted in subjective firm attachment, semiquantitative scores of the capsules were equal for both the rutile

structured as the anatase structured coating.[21] The data did not allow to indicate which crystal structure favored soft tissue attachment during the early stages of healing.
Lastly, the Turku research group compared different aging times for the sol-gel derived TiO_2 coating and this coating with 4 days immersion in simulated body fluid (SBF).[22] This was the only paper in which the bonding strength was measured objectively by pull-out force. The pull-out force was higher for coated implants (sol-gel derived TiO_2 coating with 24 h of aging time) compared to uncoated implants, but due to the large standard deviations a significant difference was not registered.[22] All the coated implants scored significantly (p-values ranging from <0.05 to <0.001) better in semi-quantitative, capsule quality and interface scores as compared to uncoated implants.[22] Neither aging time of the sol, nor immersion in SBF seemed to have any influence in the soft tissue attachment. Scanning electron microscopy of the implant surfaces showed connective tissue remnants on the coated implants, but no connective tissue on the uncoated implants. This indicated that for coated implants debonding had occurred inside the soft tissue capsule, while for uncoated implants rupture occurred at the Ti/tissue interface.[22]

All studied sol-gel derived TiO_2 coatings facilitated direct soft tissue attachment, neither aging time, coating crystal structure nor immersion in SBF seemed to influence the soft tissue attachments.[21,22,32]

Subgroup 4 – Biofunctionalized surfaces

This subgroup contains all surface modifications in which biological molecules are included at the implant surface.

Van den Beucken et al. studied the effect of two types of multi-layered DNA coatings on cp Ti (grade unknown).[33] After 4 and 12 weeks of exposure, no significant differences were observed in terms of capsular quality, quantity or interface scores with respect to coated and uncoated implants.[33] This led the authors to the conclusion that the proposed multi-layered DNA coating is histocompatible, but their utility remains unproven.[33]

Hydroxyapatite (HA) coating of transcutaneous Ti6Al4V implants improved subepithelial tissue integration in goats, but epithelial downgrowth was not reduced.[28] A HA/bioactive glass (HA/BG) coating on Ti6Al4V plates placed submucosally and supra-periostally in macaca fascicularis showed a significantly thinner capsule with better capsule quality and interface scores compared to non-coated Ti6Al4V plates after four weeks of implantation.[29] There was subjectively more adherence form the surrounding soft tissues on the HA/BG coated implants compared to non-coated implants.[29]

Enzyme treated apple pectins as a coating on Ti implant surfaces were investigated by Kokkonen et al.[34] Both versions of the modified hairy region (MHR) coating were well tolerated *in vivo*, but the in vivo response was not different in terms of inflammatory reaction compared to pristine Ti and aminated Ti surfaces.[34]

The FGF-2 apatite composite coating proposed by Mutsuzaki et al shows more promise.[35] Ti (grade unknown) percutaneous cancellous screws were implanted for 4 weeks in the medial proximal tibia of rabbits. In the FGF-2/apatite composite coating group, an inner cell monolayer was found in the capsule attached to an outer layer of fibrous tissue. This inner cell monolayer attached directly to the FGF-2/apatite composite coating. The fiber orientation of the outer fibrous tissue layer surrounding the FGF-2 apatite composite coating was 30-40° to the screw surface, because of this the authors opted to name them Sharpey-like fibers, named after the fibers connecting the teeth roots to the surrounding bone.[35] It was unclear if these Sharpey-like fibers were embedded in the FGF-2/apatite composite coating, or if these bonded onto the cell monolayer which in turn bonded onto the implant surface. In the FGF-2/apatite composite coated implants significantly less inflammation was found compared to the pristine apatite coating and uncoated implants.[35]

Growth factor coatings on TiUnite® implants placed in the subcutaneous dorsal tissue of rats for 4 and 8 weeks resulted in increased speed of connective tissue deposition onto the implant surface, most notably on rhPDGF-BB coated implants.[36] But the effect of increased groove infiltration disappeared after 8 weeks. However, the rhPDGF-BB coated implants had a significantly thinner connective tissue layer surrounding the implant compared to Emdogain® coated implants and uncoated

implants.[36] The rhPDGF-BB coating seemed to increase the maturation of the capsule: faster groove infiltration and between 4 and 8 weeks a significant decrease in thickness of the connective tissue layer.[36]

Chimutengwende-Gordon et al studied in two separate included publications the effects of hydroxyapatite (HA) coating, Fibronectin (Fn) coating and silanization (Si) in different combinations on transcutaneous implants. [37,38] In their 2011 study it was concluded that HA, HA-Fn and Si-Fn coatings did result in more favourable cell alignment (perpendicular to the implant surface) compared to polished and fibronectin coated transcutaneous implants.[37] No significant differences in the percentages of soft tissue attachment could be observed, but HA-Fn and Si-Fn coated implants scored greater soft tissue attachments scores.[37] The addition of HA coatings (HA, HA with Fn or HA with Fn and silver) to porous flanged transcutaneous implants did not result in a reduction of epidermal downgrowth compared to porous Ti.[38] An improvement of dermal soft tissue attachment could be observed in porous Ti coated with HA-Fn compared to porous Ti coated with HA only.[38] These results suggest a role for fibronectin in a coating to improve soft tissue attachment. HA coating on porous Ti seemed to reduce the beneficial effects associated with porous titanium: lesser reduction of epithelial downgrowth and less blood vessel ingrowth.[38]

Subgroup 5 – Other surface modifications

Hydrophobic nano-crystalline diamond coatings (H-NCD) and hydrophilic nano-crystalline diamond coatings (O-NCD) were compared by Kloss et al.[39] The Ti surface roughness was registered as S_a = 0.135 µm with coating, and S_a = 0.120 µm without coating.[39] The hydrophilic coating (contact angle < 10°) showed increased cell proliferation and fibronectin expression, with lower TNF-alpha expression and more elastic fibers compared to the uncoated and hydrophobic (contact angle 85-95°) coated implants.[39] A well organized, loose connective tissue zone was found in close contact to the hydrophilic coating after 4 weeks of implantation in the abdominal wall of rats.[39] These results suggest hydrophilicity as a major factor in Ti surface modifications to stimulate soft tissue attachment.

Porous Ti surfaces, achieved by plasma spraying machine finished transcutaneous implants, did not induce significant changes in terms of epithelial downgrowth and

subepithelial attachment compared to machine finished implants, as shown by Pendegrass et al.[28] A diamond like coating (DLC) on these implants induced an increase in epithelial downgrowth and a decreased attachment of the subepithelial layer.[28] However, this DLC coating deters bacterial colonization, which is a favorable outcome for transcutaneous implants on the condition that the coating is not applied on the implant part where soft tissue attachment is needed.[28]

Chimutengwende-Gordon et al. showed that 90% of the pores of porous Ti flanged transcutaneous implants in sheep were filled with soft tissues after 4 weeks of implantation.[38] This soft tissue fill was significantly more compared to drilled holes in a Ti flanged transcutaneous implant, furthermore the porous Ti had more cell nuclei within the pores and a greater density of blood vessels inside the inner pores.[38] Besides, the porous titanium resulted in reduced epidermal downgrowth.[38]

Discussion

The purpose of this systematic review was to evaluate the existing literature with respect to non-keratinized soft tissue reactions induced by Ti (alloy) implants with or without surface modifications. Using the chosen search terms and exclusion criteria, nineteen studies were included in this systematic review and none of the trials involved human subjects. The primary outcome, liquid space at the interface, was evaluated in six studies. The data of the different studies could be classified into five main surface modification categories: mechanical surface modifications, oxidative processes (e.g., acid etching, anodization, micro-arc oxidation), sol-gel derived titania (TiO_2) coatings, biofunctionalized surfaces and a subgroup for other modifications.
A liquid space at the interface was absent in most of the experimental surface treatments except for anodized fine, paste- and electropolished cp Ti and paste-polished Ti-15Mo.[8,24] Control surfaces of machined cp Ti and Ti6Al4V showed a liquid space as well, indicating the need of surface treatment to prevent this.[22,23,32]

Mechanical surface modifications of Ti alloy with R_a values of 0.5 – 1.0 µm led to subjectively favorable adhesion, whereas a smoother surface (R_a = 0.3 µm) encouraged no attachment at all, except if smoothened by acid polishing (R_a = 0.2 µm).[8,24,27,29] Whereas *in vitro* sandblasted and acid etched Ti with a far higher

average roughness and microgrooves (R_a = 22.35 μm) induced cellular adhesion of human gingival fibroblasts and murine osteoblastic cells with expression of actin filaments and nuclei on the surface.[40] This shows that the resulting thick oxide layer covering the Ti surface after acid etching (or anodization, or MAO) has a greater role in inducing soft tissue cellular attachment than average roughness alone. This was illustrated by a steep decrease in NO activity in anodized Ti implants between one and six weeks of implantation.[30] NO activity is a measure of inflammation. This lower NO activity in the capsule could be a result from the NO scavenging properties of the TiO_2 nanotubes formed by anodization.[30]

MAO on Ti6Al4V alloy implants resulted in a dramatically increased soft tissue surface attachment of 90.2% versus 3.6% in the untreated transcutaneous implants.[23] However, in this publication the roughness of the MAO treated implants was noted as coarse, and the untreated implant in that study was smooth, so this result does not indicate that there is no role for surface roughness variations in inducing soft tissue attachment. Osseotite ® treatment is a specific acid etching technique, but it did not induce significant differences in terms of soft tissue attachment, capsule quality and interface scores compared to non-treated Ti6Al4V bullets.

Sol-gel derived TiO_2 coatings all performed well, facilitating direct soft tissue attachment.[21,22,32] The sol-gel derived TiO_2 coating induces CaP on Ti substrata *in vitro* and *in vivo*, which facilitates *in situ* protein adsorption and subsequent cell reactions, thus soft tissue integration.[32,41] However, it is important to note that these results are from one research group only.

Biofunctionalization of Ti surfaces showed mixed results with respect to capsule quality, thickness, and interface scores. There is probably no clinical usefulness for the multilayered DNA coatings and MHR-A/B coatings, these coatings were found to be biocompatible, but no differences in capsule quality or inflammatory responses compared to pristine titanium were reported.[33,34] HA and HA/BG coatings showed increased subepithelial integration and a thin capsule with high capsule quality and interface scores, respectively.[28,29] HA-Fn and Si-Fn coatings did produce not-significantly greater soft tissue attachment in the (very) small preliminary study by Chimutengwende-Gordon et al, with more favorable cell alignment compared to polished

and fibronectin coated implants.[37] Addition of HA-Fn and HA-Ag-Fn coatings on porous Ti flanged transcutaneous implants did not change the outcome in terms of reduced epidermal downgrowth, percentage of epidermal attachment or soft tissue fill compared to non-coated porous Ti flanged transcutaneous implants.[38] Non-coated porous Ti flanged transcutaneous implants scored significantly better with reduced epidermal downgrowth and improved soft tissue attachment and soft tissue fill compared to straight transcutaneous Ti pins, or flanged implants with drilled holes in the flange.[38] HA coatings on porous Ti seemed to reduce the beneficial effects of the porous Ti in flanged transcutaneous implants, a reason proposed by the authors was that bacteria may win the 'race for the surface' in these cases.[38] It is unclear why the bacteria win the race in his case. The results of this research group suggest a greater role for the porous Ti in improving soft tissue attachment than for the tested coatings. Although the rhPDGF-BB coating on TiUnite ® implants increased the speed of groove infiltration in the first 5 weeks, there was no difference in the quantity of soft tissue infiltration on the long term.[36]

The hydrophilic O-NCD coating on cp Ti performed well on the secondary outcomes, reducing the inflammatory response and increasing fibronectin expression (a reflection of cell adhesion).[39] This may indicate an important role for hydrophilicity, MAO treated and anodized Ti implants inducing soft tissue attachment have lower contact angles as well.

The major difficulty in interpreting these results is the fact that one surface treatment changes several surface properties at the same time (surface topography, surface chemical composition, as well as surface wettability and energy), therefore it is not clear which change is key to an altered protein adsorption capacity and hence cellular response and tissue reaction. Furthermore, the included studies did not always give a comprehensive overview of all these surface properties, making comparisons even more difficult. This is a frequently encountered problem when evaluating the clinical outcome of (dental) implants. Rupp et al. recently presented a comprehensive review of important surface characteristics for dental implants in contact with bone, but this overview is also relevant in a broader context of implant surfaces in contact with soft tissue or blood.[42] Considering surface topography, roughness appraisal was often limited to qualitative observations and if quantitative data were available, many different

height, spatial and hybrid roughness parameters were reported (table 2) without consistently using a common parameter set. Although some guidelines have been formulated (e.g. including at least one height (such as R_a), one spatial (such as S_m) and one hybrid (such as Δ_q) roughness parameter), there is currently no consensus on the roughness parameter set that best characterizes an implant surface topography.[43] Additionally, it has been suggested that other surface roughness parameters such as skewness (R_{sk}) and kurtosis (R_{ku}) may also play an important role.[44] Moreover, nanoscaled surface features, which have recently been found to influence protein adsorption as well as cellular behavior, were not addressed in these studies.[42,45] Yet, it has been demonstrated that oral implants can exhibit very different structures on the nanoscale emphasizing the need for a surface characterization at the nanometer level (e.g. by high resolution scanning electron microscopy in combination with light interferometry) in order to correlate implant surface properties with the soft tissue response to these surfaces.[46] Another surface characteristic which was not always well described is the implant surface chemistry. However, the surface chemical composition can drive specific protein adsorption and therefore steer cellular attachment.[47] It should be emphasized that not only surface modifications based on chemical treatment or coatings, but also mechanical treatments can alter the surface chemical composition, e.g., by introducing residual particles of grinding or blasting media. Additionally, carbon contamination can originate from the ambient atmosphere or implant manipulation, which reduces the biologically available clean surface area. [42] In order to elucidate the effect of different implant surfaces on the biological response thereby also excluding any effects caused by impurities, it is important to also document chemical changes at the surface. Surface analytical techniques, such as X-ray photoelectron spectroscopy or ToF-SIMS, are generally preferred over other elemental analysis techniques as energy dispersive X-ray spectroscopy, because of the larger interaction volume of the latter. Many of the included studies did not describe the implant surfaces' wetting behavior, although it is now well accepted that there is a distinct effect on the protein conditioning film formed during the initial implant/blood contact, and consequently, on the cell/implant interactions.[42] Wettability is commonly determined by contact angle measurements using the sessile drop method, which can be challenging on complex shaped implant surfaces. Alternatively, tensiometry has been suggested in order to determine contact angles from force measurements during immersion in simulated bioliquids of known surface tension.[42] Finally,

a more complete characterization of the wetting behavior can be obtained by contact angle measurements in different polar and apolar liquids, so that the total surface free energy and its polar/apolar or acid/base parts can be calculated using the Young equation.[48] It is worth noting that surface roughness and wettability are interrelated, especially when evaluated at the nanoscale and synergistic effects of nanostructures surfaces and hydrophilicity on the bioresponses have been observed, but are not well understood yet.[42] In addition to inconsistency in the surface properties reported, often very different methods for evaluating soft tissue reaction layers were used, leaving ample room for discussion about a possible influence on the results. An often-used method for evaluating the capsules around implants is the method proposed by Jansen et al.[18] These researchers consider a thin, fibrous capsule, resembling non-injured connective tissue (low fibroblast count; no inflammatory cells present) as ideal. This may be true, but the semiquantitative and qualitative scores obtained require careful interpretation. A capsule may be viewed as a scar developing over time, differing greatly at 1 week, several weeks, or months after implantation. The number of inflammatory cells will subside over time, automatically raising the capsule quality score. A good interface score has fibroblasts in intimate contact with the implant surface, but a good semiquantitative score equates with few fibroblast layers. These principles are not necessarily in conflict with one another, but such scores are highly dependent on *in situ* implant duration. The ideal titanium-soft tissue interface then remains in question. For example, breast augmentation implants are plagued by capsular contraction. This complication occurs less often in polyurethane coated compared to pure silicone implants.[49] A suspected reason is the polyurethane bio-integration layer. Its multidirectional collagen fibers interdigitate with the textured polyurethane and attach to layer-2 collagen. The contracting forces of layers 2 and 4 (both largely circumferential collagen fibers) are nullified by the sponginess of polyurethane, thus hindering contraction of the capsule.[50,51] Due to gradual loss of polyurethane, this layer is attenuated over time, so the collagen fibers ultimately revert to a more circumferential orientation. In Ti implants, capsular contraction does not pose a real problem for the shape of the implant. However, a contracted capsule could result in a change of shape of the overlying soft tissues resulting in an esthetically displeasing result.

The Sharpey-like fibers described by Mutsuzaki et al. ostensibly constitute a near-perfect implant-soft tissue interface.[35] These fibers were discovered during their research into FGF-2 composite apatite coating of a percutaneous cancellous screw made of cp (grade unknown) Ti. Compared with non-coated counterparts, the FGF-2 coated screws provoked significantly less inflammation. Other research by the above group has also indicated that this same coating layer induced apposition of high-quality bone around osteosynthesis screws, indicating the high potential of these coatings should be further investigated [52]. If such coating indeed induces bone apposition and soft tissue integration, the net effect (e.g., in facial contouring) will depend on the speed of proliferation. If a peri-implant bony apposition develops, the net implant effect may be a larger-than-planned volume; but implant stability may be impaired, if a soft tissue bridge develops between bone and implant. In our practice, we have already witnessed bony apposition to a subperiosteally placed jaw-angle augmentation implant (plasma surface activated grade 23 Ti (Ti6Al4V ELI (extra low interstitials)), see Figure 2), without clinical aesthetic complaints.

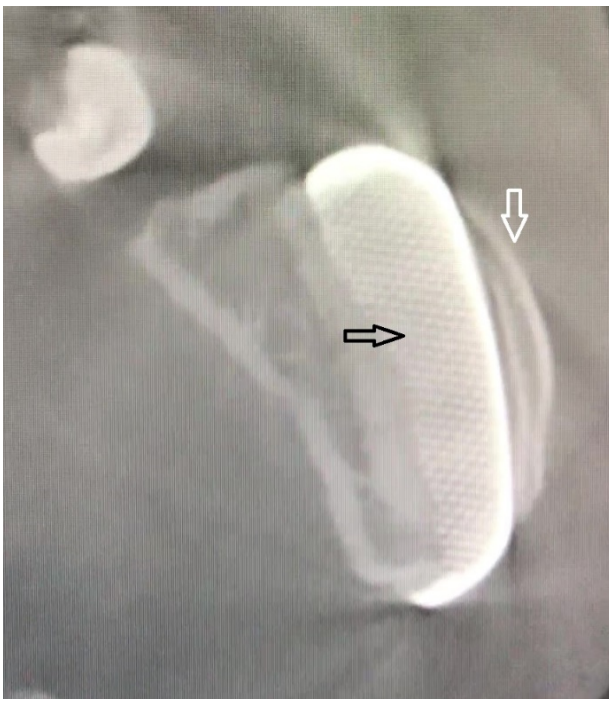

Figure 2 Calcification on subperiosteally placed jaw angle augmentation implant White arrow indicating calcification, black arrow indicating implant

The design of this systematic review, despite its broad scope, excludes all studies of the Ti-gingiva interface. An abundance of research on gingival reaction to Ti dental implant abutments is available in dentistry archives.[2] We chose to ignore these studies, because our interest is limited to the reaction between non-keratinized soft tissues

(periosteum, muscle, fat, connective tissue, dermal/subdermal tissues, etc.) and patient-specific 3D-printed Ti implants and Ti osteosynthesis material. This makes our review weaker in one sense (fewer research papers included), but stronger in another (no skewing of results by unwanted data on keratinized soft tissues). Surprisingly, none of the selected studies have investigated the effects of 3D-printed grade 23 Ti ELI, which is the material of choice for modern facial recontouring implants.

Conclusion

In this review, 19 publications met our inclusion criteria, all varying considerably in design (especially measured outcomes), but none involving humans. Six studies reported on the primary outcome: presence or absence of a liquid space at the interface. Machining Ti implants to a roughness between R_a = 0.5 – 1.0 µm is shown to induce soft tissue adhesion, as does porous sintered Ti. Smoother surfaces, except for acid polished and anodized Ti (R_a = 0.2 µm), prevent soft tissue adhesion. MAO treatment of Ti6Al4V dramatically increases the percentage of soft tissue adhesion to the implant surface. All versions (although only studied by one research group) of the sol-gel derived TiO_2 coatings induced better soft tissue attachment compared to non-coated implants, neither aging time, crystal structure nor immersion in SBF seemed to influence this. Ultimately, FGF-2/apatite composite coating may well impart a near-perfect implant-soft tissue interface. Although bonding strength was not objectively measured, FGF-2 coated percutaneous cp Ti screws are known to display soft tissue attachment via Sharpey-like fibers.

Further studies of the interface between Ti alloy implants and surrounding soft tissue elements are recommended, especially a standardized instrument for evaluating soft tissue attachment onto these implants and a standardized characterization and description of the Ti surface parameters, to reliably correlate both sets of data. Furthermore, an analysis of the cost-effectiveness of these surface treatments and coatings is also advised to evaluate if the observed preclinical benefits are indeed relevant clinical benefits and worth the extra investment for the manufacturer and, ultimately, the patient.

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Chapter VIII: Discussion

General discussion

Oral rehabilitation plays a crucial role in ensuring a high quality of life and overall well-being[1-2]. However, oral rehabilitation for an extremely atrophic maxilla is a complex process that requires careful planning and coordination between the patient, the dentist, and other healthcare professionals. A thorough evaluation of the patient's oral health and overall health status is necessary to determine the best treatment option. Unfortunately, for patients with severe jaw atrophy, very limited options are available.

Different regenerative techniques can be employed to augment the alveolar ridge in terms of both vertical and horizontal dimensions. Autologous bone harvesting offers the option of using different anatomical sites to obtain bone grafts for onlay placement. Typically, autologous grafting of calvarial or iliac bone is employed in cases of severe alveolar ridge atrophy. This method is widely utilized and is considered by some experts as the "gold standard"[4-6]. The feasibility of bone grafting has been studied extensively and many reports about autologous bone grafting and its use in oral rehabilitation, have been published[4-6]. However, there is limited knowledge regarding the patient's perspective[4-8]. A randomized controlled trial by Wortmann et al. examined patient satisfaction and compared the effect of calvarial and iliac bone grafts in 20 consecutive edentulous patients who had less than 3 mm of bone height in the maxillary sinus area and less than 2 mm of bone width in the anterior maxillary area[9]. A bilateral maxillary sinus floor augmentation and reconstruction of the width of the maxilla was carried out in all patients. Twelve months after receiving their implant-supported maxillary overdentures the mean visual analog scale (VAS) score was 93 out of 100, indicating high satisfaction. The mean Oral Health Impact Profile (OHIP-49NL) score decreased from 78.80 preoperatively to 16.00 post-treatment. However, several patients experienced postoperative complications, including infection at the donor site, scar formation and loss of sensitivity. Even more, three patients reported walking difficulties after one year. In a cross-sectional retrospective cohort study, Gjerde et al. (2020) also evaluated patient-reported outcomes in 44 patients (with a mean age of 61.2 years ± 13) who underwent maxillary alveolar ridge augmentation using anterior iliac crest grafting[10]. They found a mean OHIP-14 score of 8.4 ± 9.7, indicating a favorable oral health-related quality of life and patient satisfaction. However, bone grafting was unsuccessful in 10% of the patients. Furthermore, the rate of

implant survival, along with prosthetic rehabilitation, was reported to be only 70.1% after one year. In addition, patients required an average hospitalization period of 4.3 days and reported an average of 20.2 days of sick leave, resulting in both financial costs for the health service and inconvenience for the patient. The use of calvarial bone as an alternative to iliac crest bone has proven to be highly valuable[11-13]. Chiapasco et al. (2018) investigated 72 patients, from 1998 to 2014 with severe jaw atrophy reconstructed with autogenous calvarial bone blocks covered with bovine bone granules and collagen membranes. The follow-up ranged from 3 to 19 years (mean: 8.1 years) and a survey, adapted from the OHIP-14 survey, was provided to the patients to assess their satisfaction. At the latest recall, 90% of the patients were satisfied. However, one out of ten patients indicated not wanting to undergo the surgical protocol a second time due to the associated morbidities. In a meta-analysis conducted by Wortmann et al. (2022), patient-reported outcomes were compared between autogenous iliac bone and calvarial bone harvesting[14]. The study included 206 patients who underwent augmentation using calvarial bone, and their satisfaction levels were assessed using the VAS. Patients were satisfied with the result and a score ranging from 8.8 to 10 was reported. Additionally, a total of 696 patients received anterior iliac bone grafts, and overall patient satisfaction was reported with a VAS score ranging from 9.5 to 10. When compared to the "calvarial bone harvesting group", no statistically significant difference was observed.

While bone regenerative techniques have shown excellent results in achieving long-term implant success in the atrophied maxilla[7-14], there are several drawbacks associated with reconstructing the atrophic maxillary crest that are often not thoroughly discussed in the literature. One major drawback of utilizing free grafts is the unavoidable disruption of microcirculation during the harvesting process, hindering the reestablishment of graft circulation. Revascularization of the graft is crucial for osteogenesis and graft survival, but it takes time, during which the vitality of osteocytes is often compromised[15]. Consequently, areas of necrotic bone may develop, resulting in undesirable and unpredictable graft resorption. Significant resorption can affect the esthetic and functional stability of implants, necessitating additional bone augmentation procedures to ensure sufficient volume for reimplantation. Furthermore, the success of bone augmentation relies on the osteogenic potential, which varies among individuals and diminishes with age, potentially leading to an even more

increased rate of bone resorption[16]. The extent of resorption also strongly depends on the site from which the bone was harvested. Onlay grafts harvested from the iliac crest have been reported to exhibit an average volume decrease of 50% within six months following placement in the atrophied maxilla[17]. A retrospective study by Öztürk et al. (2021) found a mean graft resorption rate of 32.42% (± 19.39) in the maxilla after 3 to 6 months postoperatively[18]. Same was found in the study of Sbardone et al. (2011) where an average of 35-51% resorption was reported after 1 year post operative[19]. When compared to iliac bone grafting, calvarial bone grafts showed far less resorption. Still, resorption was present and its degree remained mostly unpredictable. Fourcade et al. (2019) found a mean resorption of 25% of calvarial (parietal) bone for pre-implant reconstruction of maxillary alveolar ridges after four months[20]. Chiapasco et al. (2018) reported a mean peri-implant bone resorption up to 4.87 mm in height in patients when calvarial bone were used[13]. Smolka et al. (2006), found a mean volume reduction of 16.2% at 6 months postoperatively and 19.2% at one year follow-up.

Zygomatic implants (ZI) offer an alternative to bone grafts and have demonstrated a high success rate and predictability in the past[22-24]. However, the success rate of ZI's has not been so extensively described, and only few clinically applicable criteria for success are given in literature. The definition of "success" is often based on implant survival rather than patient satisfaction or quality of life, which are important factors that are often overlooked in reporting outcomes. Few studies have analyzed the quality of life and patient satisfaction specifically in relation to maxillary atrophy[22-25]. An exception is the study by Fernández-Ruiz et al. (2021), which examined patients' satisfaction and quality of life in 40 patients rehabilitated with a combination of zygomatic and conventional implants in the premaxilla[26]. Their findings showed a mean follow-up period of 19.40 ± 4.37 months and a reported mean VAS score of 18.48 ± 3.42.

Confronted with extreme maxillary atrophy, clinicians have focused on traditional approaches, such as implant placement in remote bone areas (e.g., zygoma) or local/distant augmentation using a variety of materials and techniques. The objective in each of these approaches has been to establish a connection between endosseous fixtures and suprastructures, adhering to the recognized "gold standard" in the field.

However, these methods face limitations and can be associated with a significant patient morbidity as described above. Subperiosteal implants were initially developed around 80 years ago as a solution to address the challenges of stabilizing and retaining full dentures in patients with significant ridge resorption. Although conventional subperiosteal implants have demonstrated long-term survival they have also encountered several failures for various reasons[28].

Subperiosteal implants, are now experiencing a resurgence in popularity. Digital technology has revolutionized the field of dentistry, enabling the manufacturing of patient-specific implants with unprecedented precision. In particular, 3D printing has sparked a renewed interest in exploring and reevaluating earlier concepts, such as subperiosteal implants. Titanium, renowned for its biocompatibility and mechanical strength, can now be utilized in the additive manufacturing process, allowing to produce intricately designed subperiosteal implants. The integration of 3D planning software facilitates meticulous preoperative planning, ensuring optimal fit and functionality of the implants within the patient's unique anatomical structure. This evolution has given rise to a new "high-tech" subperiosteal implant known as the additively manufactured Subperiosteal Jaw Implant (AMSJI).

Patient-reported outcome measures for AMSJI demonstrates similar satisfaction rates to autogenous bone augmentation and zygomatic implant placement according to our two studies[29-30]. First, a multicenter prospective study was carried out and involved fifteen consecutive patients[29]. Follow-up took place for 1 year and patients were interviewed using a study protocol and underwent clinical and radiographic examinations preoperatively (T0) and at 1 (T1), 6 (T2), and 12 (T3) months after permanent upper prosthesis placement. Over time, both the mean overall OHIP-14 score and the mean individual domain scores decreased. The OHIP-14 score at T0 was 17.20 (SD 6.42). A statistically significant difference was observed when comparing T0 to T1 (mean 8.93, SD 5.30; P = 0.001). At T3, the mean value was 5.80 (SD 4.18), also showing a statistically significant difference when compared to T0 (P = 0.001). General satisfaction was assessed using the numerical rating scale and a mean of 49.93 at T1 was reported. This which was slightly lower than the patients' expectation prior to treatment at T0 (52.13). However, there was an overall increase in satisfaction at T3 (mean 53.20) compared to T0. Another retrospective study involving forty

patients who underwent maxillary rehabilitation with AMSJI evaluated patient satisfaction and oral health using the OHIP-14 and numerical rating scale (NRS)[30]. This study included fifteen men (mean age: 64.62 years, SD 6.75 years) and twenty-five women (mean age: 65.24 years, SD 6.77 years), with an average follow-up time of 917 days (SD 306.89 days) after AMSJI installation. Patients reported a high mean OHIP-14 score of 4.20 (SD 7.10) and a high mean overall satisfaction score based on the NRS of 52.25 (SD 4.00) was seen. It is worth noting that a previous study by Dahl et al. reported an OHIP-14 score of 4.1 in the Norwegian adult population, consisting of 2441 patients[31]. The slightly lower AMSJI patients' satisfaction score could be attributed to the fact that all patients had oral compromises and limited options for obtaining fixed teeth. Many of them had experienced oral problems in the past and had undergone multiple interventions for oral rehabilitation. Their satisfaction with obtaining fixed dentures directly influenced their perceived oral health condition, which explains their positive reported oral health-related quality of life.

AMSJI offers the advantage of being readily placed in private clinics, making it accessible for medically compromised and/or elderly patients without the need for hospitalization, thus reducing the burden on society (depending on the national healthcare system). AMSJI installation be done in an outpatient clinical setting with local anesthesia alone. Hospitalization is not needed, and patients typically report only mild pain that can easily be managed with common pain relievers such as acetaminophen (paracetamol) and NSAIDs. While postoperative complications can occur with AMSJI, they should not be compared to the more significant complications, such as penetration into the eye socket or infratemporal fossa that is described following the placement of zygomatic implants[27]. AMSJI presents itself as a patient-centric alternative when compared to zygomatic fixtures and autogenous bone augmentation procedures. Unlike the latter techniques, AMSJI entails a single surgical procedure that offers immediate postoperative chewing function. This stands in contrast to the two-step protocol involved in bone regeneration methods. In such protocols, an initial augmentation is performed, followed by a waiting period of approximately three to four months before endosseous implant placement, assuming the graft has not undergone resorption. Subsequently, additional time is required for implant integration into the bone, leading to further delays in the ultimate placement of the prosthesis.

The phenomenon of uncontrollable and unpredictable resorption following autologous bone grafting continues to pose a significant challenge. For AMSJI, the effect on maxillary bone morphology was studied[32]. A cohort of fifteen patients presenting with severe maxillary atrophy, classified as Cawood-Howell Class V or greater, underwent evaluation through periodic (cone beam) computed tomography scans at two-time intervals: one month (T1) and twelve months (T2) after the installation of the final prosthesis for restoration of masticatory function. Fixed evaluation points were predetermined, and a surface comparison was conducted to quantify and visualize the impact of AMSJI on the surrounding bone. Across six specified reference points on the crest, an overall mean negative bone remodeling of 0.26 mm (with a standard deviation of 0.65 mm) was observed. Additionally, minor bone loss (mean resorption of 0.088 mm, with a standard deviation of 0.29 mm) was detected at the supporting bone specifically in the wings and basal frame regions. This amount resorption rivals the results of Koodaryan and Hafezeqoran (2016) who found a mean annual bone loss of 0.2 mm after one year of implantation[33]. The elevation of the mucoperiosteal flap is recognized as a potential contributing factor to the occurrence of resorption[34]. This surgical procedure exposes the alveolar bone, resulting in a partial deprivation of oxygen to the underlying tissue. Due to this hypoxic environment, the activity of osteoclasts is promoted. Consequently, bone resorption takes place, followed by a remodeling process. This may explain a portion of the observed crest resorption described in our series.

The biological and chemical interaction between titanium (Ti) and bone has been extensively studied and thoroughly characterized, particularly in the context of dental implants[35-37]. However, the long-term stability of titanium implants is not solely determined by their osseointegrative capacity. Like traditional dental implant-based rehabilitation procedures, the survival and success of these implants also relies on the health of the surrounding soft tissues[38]. The surface of the implant plays a vital role in eliciting a favorable cellular and tissue response surrounding the implants[39]. For endosseous implants, it is recommended to have a region of attached keratinized gingiva around the implant shoulder, as this provides a biological seal[36-39]. The absence of this connective tissue barrier around dental implants is believed to allow the infiltration of pathogenic bacteria, leading to persistent mucositis and peri-implantitis and eventual failure of the endosseous implant[38-40]. For SI, the value of the surrounding

soft tissues is much less understood and studied. In modern subperiosteal implants, such as those studied by Korn et al., soft tissue recessions are frequently observed, with partial exposure of the underlying framework found in 47.36% of patients[40]. We undertook a multinational multicenter study to assess soft tissue response after oral rehabilitation with AMSJI in the maxilla with the goal to identify risk factors for soft tissue recession[41]. The study comprised a total of 40 participants, consisting of 15 male subjects (mean age: 64.62 years, SD ± 6.75) and 25 female subjects (mean age: 65.24 years, SD ± 6.77). All participants had previously undergone bilateral placement of AMSJI at least one year before the study commencement. Partial exposure of the arms was observed in 26 patients; however, patients did not experience this as a functional or aesthetic impediment. Our study indicated that biotype is a significant risk factor ($p < 0.001$) and plays a crucial role in the development of soft tissue recessions. This finding aligns with previous research indicating that individuals with a thin periodontal phenotype are more prone to experiencing soft tissue recessions, and that thin buccal peri-implant soft tissues are associated with an elevated risk of mucosal recession[42]. In cases where a patient exhibits a thin biotype, the potential for conversion can be achieved through the utilization of soft tissue flaps, specifically gingival and palatal advancement flaps. Also, the implementation of a beveled palatally shifted incision line enables the translocation of keratinized mucosal tissue towards the buccal aspect, thereby enhancing its thickness in this region. Additionally, alloplastic products such as collagen matrices have been employed as a means to augment soft tissue thickness, eliminating the requirement for supplementary procedures. These materials are positioned between the primary structure and the gingival flap during the implantation process, constituting an all-in-one intervention.

Another significant risk factor that was defined was the presence and severity of mucositis. Subperiosteal implants offer notable advantages over conventional endosseous implants, particularly in terms of the site of mucosal penetration, which is situated distant from the internal fixation of the implant framework, as observed in zygomatic implants. As a result, the inflammatory state of the keratinized or non-keratinized tissue remains confined to a local area and does not readily affect the bone-like fixation points. This observation may provide an explanation for why certain patients manifest mucositis.

Implantation of subperiosteal implants is considered clean-contaminated surgery. For this reason, safety measures need to be taken to minimize bacterial invasion and/or colonization of the SI. Meta-analyses report a statistically significantly lower number of dental implant failures when preoperative prophylactic antibiotics are administrated[43-45]. Three grams orally of amoxicillin is recommended one hour before the intervention, when carried out under local anesthetics[44-45]. Prolonging antibiotic prophylaxis for 24-48 h after surgery was associated with the highest prevention rate of surgical site infection[45]. If peri-implant mucositis occurs, mechanical debridement (supra- and subgingival) with temporary removal of the supra-structure is the treatment of choice as it considerably reduces bacterial levels[46]. Besides professional mechanical debridement, the use of an oral irrigator with 0.06% aqueous chlorhexidine solution reduces peri-implant mucositis over a 3-months period[47]. A treatment with amoxycillin and metronidazole combination is advised as chronic periodontitis is often caused by Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Prevotella intermedia and Treponema denticola.

Treatment of subperiosteal peri-post mucositis requires specific - open sky - mechanical debridement. The biofilm is removed after flap raising with a soft Teflon tip piezo device. The wound is irrigated for 2 minutes with 3% peroxide. The exposed titanium is treated for 2 minutes with phosphoric acid 35%. The cavity is rinsed with aqueous chlorhexidine solution. Culture and testing are required for the treatment of deep soft tissue infections and immediate amoxicillin and metronidazole therapy is necessary. Quinolone and rifampicin therapy can be considered second choice when culture shows resistance against penicillin or allergy is present.

There remains a risk of failure associated with the technique described in this thesis. However, in the event of complications necessitating removal, the abutment can be detached from the main frame by cutting the specifically designed weak areas using rotating instruments. Several abutments can be removed prior to system failure. Like zygomatic implants, the most cranial fixation of the AMSJI remains unaffected in the presence of peri-mucositis. If complete removal of the AMSJI becomes necessary, a replica can be generated through three-dimensional printing since the stereolithographic (STL) files are permanently stored in a digital database. Furthermore, in cases of total loss of the AMSJI, none of the anatomical structures are damaged. The frame

can be reprinted, and if the soft tissues are well healed, the AMSJI can be reinstalled while reutilizing the existing suprastructure and denture. This restorative approach is not feasible with treatments involving zygomatic implants or the “All-on-Four concept” as they unfavorably impact the anatomy, necessitating the manufacture of new suprastructures and dentures.

Limitations

Within the context of this thesis, a comprehensive analysis of the inherent limitations associated with the research has been conducted and addressed in each respective chapter. A concise summary encompassing these limitations is described hereafter.

One significant limitation pertains to the sample size. Given the novelty of subperiosteal implants, it is challenging to gather a large patient population. Consequently, the relatively small patient population described in this thesis limits the generalizability of the findings to a wider population. Furthermore, the focus of this research was predominately on short-and medium-term outcomes, limiting the understanding of the long-term performance, viability, stability, and complications of subperiosteal implants. Longer follow-up periods, ideally extending over multiple years, would provide a more comprehensive assessment of the implant long term results. Furthermore, the absence of a control group poses a limitation in assessing the effectiveness and outcomes of subperiosteal implants compared to alternative treatments. The inclusion of a control group would allow for comparative analysis, providing valuable insights into the advantages and limitations of subperiosteal implants.

Frequently, a high standard deviation (SD) was seen when results are described in several of the above-mentioned chapters. A large SD in a dataset signifies a pronounced degree of dispersion, indicating a substantial variability from the mean. This implies a wider spread of values and it suggests a noteworthy heterogeneity among participants. Such variability can be critical when assessing treatment efficacy, patient responses to the intervention, or the overall reliability of clinical measurements potentially influencing the study's conclusions. This dispersion may point to variations in individual responses to the intervention and highlights the need for further exploration into patient subgroups or factors contributing to the observed diversity.

The variability in surgical technique also poses a significant limitation. Multiple surgeons and centers introduces differences in surgical approaches, nuances, and levels of expertise. These variations can confound the study outcomes, affecting factors. Surgeons with varying experience and skill levels may yield different results, and factors like the learning curve associated with a specific technique can further contribute to variability. Methodological constraints also introduce limitations. These constraints involve limitations in data collection techniques, such as the accuracy of measurements or the reliance on subjective assessments. Additionally, limitations in imaging modalities or other assessment tools can impact the comprehensiveness of the data gathered, potentially limiting the insights derived from the study.
Recognizing and acknowledging these limitations is crucial for a balanced interpretation of the research findings. Furthermore, these limitations serve as opportunities for future investigations, highlighting areas where methodological refinements and larger-scale studies can enhance the understanding of subperiosteal implants and their clinical implications.

Future directions

Over the years, significant research and literature have been dedicated to studying the osseointegration of titanium implants. However, comparatively less attention has been given to the integration of soft tissue with titanium implants, despite the critical role of a robust soft-tissue seal in ensuring optimal implant survival. Ideally, the interface between the epithelium and the implant should consist of a thin, soft tissue capsule with minimal presence of inflammatory cells and fibroblasts. Furthermore, the collagen fibers should be oriented perpendicularly or obliquely to the implant surface to achieve direct adherence between the soft tissue and the implant. The implant surface plays a crucial role in promoting a favorable cellular and tissue response around the implants. Ti and its alloys are widely recognized for their excellent biocompatibility, primarily due to the presence of a stable oxide layer on the surface, which facilitates direct bone apposition and osseointegration. However, establishing a permanent direct attachment of soft tissue is more challenging. Animal experiments have revealed the existence of a barrier epithelium in contact with the TiO2 surface through hemidesmosomes, but collagen fibers remain parallel to the implant surface, preventing true chemical and mechanical bonding[48]. Surface modifications, such as machining Ti implants to a roughness of Ra = 0.5-1.0 μm or using porous sintered

Ti, can induce soft tissue adhesion[49]. Smoother surfaces, except for acid-polished and anodized Ti (Ra = 0.2 μm), hinder soft-tissue adhesion[49]. Treatment of Ti6Al4V with Microarc Oxidation (MAO) significantly enhances soft-tissue adhesion to the implant surface[50]. Different variations of sol-gel derived TiO2 coatings have demonstrated improved soft-tissue attachment compared to non-coated implants, with aging time, crystal structure, and immersion in simulated body fluid showing minimal influence on the results[51]. Porous titanium coatings with pore sizes below 250 μm do not support dermal fibroblast tissue attachment, whereas larger pores (>700 μm) facilitate vascularized soft-tissue infiltration and cell attachment[52].

Surface modification of titanium (Ti) implants is a proposed method to improve the integration of soft tissues with the implant. Conventional techniques like bead blasting, etching, or anodization can change the original surface of the substrate. Alternatively, coatings provide complete coverage of the pristine metal surface with a biologically active material, facilitating interaction with host cells while preserving the original surface. Various coatings have been studied, including those that mimic components of living tissue such as calcium phosphate coatings or biological coatings composed of extracellular matrix components or growth factors. These coatings have been investigated for their ability to activate epithelial and fibroblast functions, which are crucial for soft tissue integration. One promising approach involves the physical entrapment of fibroblast growth factor-2 (FGF-2) within biomimetically deposited calcium phosphate coatings. In vitro release testing has demonstrated controlled delivery of FGF-2 over an extended period. Furthermore, in vivo experiments have confirmed the beneficial effect of FGF-2 on soft tissue attachment to the implant surface. Researchers have reported the formation of structures resembling Sharpey's fibers, which are inclined at 30-40 degrees to the implant surface. These fibers play a significant role in anchoring soft tissues to the implant and contribute to improved integration[53].

Despite the presence of promising results, no studies to date were able to demonstrate the formation of an implant-soft tissue seal that matches the complexity observed in natural conditions. Consequently, it is highly recommended to conduct further long-term in vivo research with a specific emphasis on comprehensive surface

characterization, detailed and thorough analysis of soft tissue characteristics, and establishing correlations between these factors.

To advance our understanding of implant-soft tissue integration, future research should employ comprehensive surface characterization techniques to explore the intricate features and properties of implant surfaces. This includes analyzing surface roughness, topography, chemical composition, and the presence of specific functional groups. By obtaining a more detailed understanding of the surface characteristics, researchers can gain insights into their impact on soft tissue attachment and integration. Furthermore, detailed in-depth analyses of soft tissue responses are crucial to unravel the mechanisms involved in the implant-soft tissue interaction. This involves investigating cellular responses, extracellular matrix composition, collagen organization, inflammatory reactions, and the formation of cellular adhesion structures. By conducting comprehensive analyses, researchers can gain a deeper understanding of the factors influencing soft tissue integration and identify potential areas for improvement. Importantly, establishing correlations between surface characteristics and soft tissue responses is essential to guide the development of implant surfaces that facilitate optimal soft tissue integration. By investigating the relationship between specific surface features and the formation of a functional implant-soft tissue seal, researchers can identify key design principles for enhancing implant success.

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Curriculum Vitae

Casper Elias Van den Borre was born in Aalst, Belgium in 1993. He obtained his bachelor's degree in medicine from the University of Hasselt in 2015 and his master's degree in medicine from the University of Antwerp in 2018. Immediately after graduating, Casper was given the opportunity by Prof. Maurice Mommaerts to enroll as a PhD student at the Vrije Universiteit Brussel. Between 2018 and 2021 Casper attended the University of Gent where he obtained his bachelor- & master's degree in dentistry while combining his PhD study. He then started his clinical training in Oro-Maxillo-Facial Surgery at the Universitair Ziekenhuis Brussel in the "European Face Centre", under the supervision of Prof. Maurice Mommaerts. From August 2022 till August 2023, Casper was trained under supervision of Drs. Hylke Schouten and Prof. Dr. A.G. Becking at the Spaarnegasthuis ziekenhuis, Haarlem, the Netherlands. Currently, Casper rejoined Prof. Mommaerts as a third-year trainee in cranio-maxillofacial surgery at GZAntwerpen/Face Ahead Surgicenter.