Surgical Innovations of Bone Anchored Hearing Implants

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A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Doctor of Philosophy

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February 2021

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Abstract

The rapidly evolving field of auditory osseointegrated implants has seen many innovations that have rehabilitated more hearing-impaired individuals worldwide. Improved surgical approaches to bone anchored hearing implantation has successfully decreased operative time and peri-operative complications, while wider screws with roughened surfaces have shown improved implant stability and resulted in lower implant loss rates.

Evaluation of the integrity of the bone-implant interface of bone anchored hearing implants is warranted as it could aid clinicians to decide the timing of loading of the sound processor, prevent implant extrusions, and monitor post-operative implantation success. The advent of a novel tool determining the stability of the anchorage is needed.

This thesis investigates rates and reasons behind bone anchored hearing implant extrusions. A novel implant stability tool was compared with traditional mechanical testing modalities in a cadaveric laboratory evaluation and peri-operative trends were studied in a prospective clinical cohort.

Additionally, the thesis investigated skin tolerability following bone anchored hearing implant surgery by comparing different surgical approaches and various classification scales. The final portion of the thesis touches upon the benefits of novel transcutaneous systems.

Through a systematic review, the identified rates of bone anchored hearing implant extrusions are 7.3%, more commonly seen in pediatric recipients. The studies included in this thesis identifies reasons behind implant extrusions that should be considered when evaluating patient's candidacy for osseointegrated auditory implant surgery. A clinical cohort study investigating peri-operative implant stability quotient through a novel device suggests that sound processor loading can be performed as soon as the skin is healed for adults but warrants a wait period of 6 weeks for children.

This same tool was further investigated in a human cadaveric bone laboratory examination where mechanical testing helped better understand what the tool measures. Skin tolerability classification scales were compared. The studies show that a great variability exist in determining skin reactions between raters. To avoid skin reactions resulting from the percutaneous nature of auditory implants, transcutaneous systems are increasingly emerging. The Sophono^{TM} transcutaneous bone conduction device shows promising functional improvement, no intra-operative complications and minor post-operative skin related complications. If suitable, the device could be a proposed solution for the rehabilitation of hearing for those meeting eligibility criteria. However, a wearing schedule must be implemented in order to reduce magnet-related skin complications.

Résumé

Les implants auditifs ostéointégrés dans l'os crânien a vu de nombreuses innovations qui ont permis la réhabilitation d'un demi-million de personnes malentendantes à travers le monde. Des approches chirurgicales améliorées ont réussi à réduire le temps opératoire et les complications péri-opératoires, tandis que des implants plus larges avec des surfaces rugueuses ont montré une meilleure stabilité de l'implant et ont entraîné des taux de perte d'implant très faibles.

L'évaluation de l'intégrité de l'interface os-implant des implants auditifs à ancrage osseux est important car elle pourrait aider les cliniciens à décider le moment de couplage du processeur de son, à empêcher les extrusions d'implants et à déterminer le succès de l'implantation post-opératoire. Un nouvel outil qui pourrait déterminer la stabilité de l'ancrage est nécessaire pour faire des décisions importants en clinique.

Cette thèse examine les taux et les raisons des extrusions d'implants auditifs ancrés dans l'os et propose un nouvel outil de stabilité étudié dans une évaluation cadavérique en laboratoire et dans une cohorte clinique prospective. De plus, la thèse a étudié la tolérance cutanée après la chirurgie d'implant auditif à anchorage osseux en comparant différentes approches chirurgicales et diverses échelles de classification de l'état cutané du site de l'implant. Les derniers chaptire de la thèse aborde les avantages des nouveaux systèmes transcutanés.

Grâce à une revue systématique, les taux d'extrusions d'implants auditifs ancrés dans l'os sont de 7,3%, plus fréquemment observés chez les candidats pédiatriques. Les études incluses dans cette thèse identifient les raisons des extrusions d'implants qui doivent être prises en compte lors de l'évaluation de la candidature du patient à la chirurgie. Une étude de cohorte clinique examinant le quotient de stabilité péri-opératoire de l'implant suggère que le couplage du processeur de son peut être effectuée dès que la peau est guérie pour les adultes, mais justifie une période d'attente

de 6 semaines pour les enfants. Ce même outil a été étudié dans une investigation cadavérique en laboratoire où des tests mécaniques ont permis de mieux comprendre ce que l'outil mesure. Les échelles de classification de la tolérance cutanée ont été comparées. Les études montrent qu'il existe une grande variabilité des interprétations des réactions cutanées après la chirurgie. Pour éviter les réactions cutanées résultant de l'implant percutanée, des systèmes transcutanés émergent de plus en plus. Le système de conduction osseuse transcutanée Sophono^{TM} présente une amélioration de l'audition prometteuse, aucune complication post-opératoire. Le système pourrait être une solution proposée pour la réhabilitation auditive des personnes répondant aux critères d'éligibilité. Cependant, un calendrier de port doit être mis en place afin de réduire les complications cutanées liées aux aimants.

Acknowledgments

I would like to thank my supervisor, Dr. Sam J Daniel, for giving me the opportunity to learn and thrive at McGill University. His guidance and mentorship in the last 8 years have been pivotal in shaping my character and discovering my future ambitions and life goals. I am eternally grateful to have witnessed and contributed to the intellectual challenges that advance science and medicine to improve health care. Dr. Daniel shows us that when scientists and physicians work together, the power of basic science surfaces in clinical practice and innovative approaches coalesce to yield outcomes that improve the quality of life of children.

I would like to express my gratitude to Dr. Bettina Willie, who's invaluable support, collaboration and guidance made this thesis possible. Thank you for always making time to meet students individually and offer your humble aid when students are facing uncertainties. Thank you to the members of her lab, Dr. Zimmermann, Dr. Rummler, Alice, Kyle, David, Isabela, Joseph, Mehdi, and Catherine for their important contributions.

A sincere gratitude to the Department of Pediatric Surgery for their support, in particular Dr. Jean-Pierre Farmer who has provided invaluable input and support throughout my academic endeavours at McGill University. It is truly humbling to witness Dr. Farmer's humanitarianism, generosity and efforts towards making the Montreal Children's Hospital a warm place for scientific innovation and state-of-the-art care. Thank you to Dr. Roy Dudley for your patience, and collaboration on various impactful projects. Thank you to the members of my advisory committee, in particular the chairman, Dr. Jacques Lapointe, for your invaluable guidance during my advisory committee meetings. A special thanks to Sharon Turner from Experimental Surgery for her constant support.

Dr. Walid Mourad, thank you for teaching me that passion isn't innate; that it's developed, for encouraging me to pursue my graduate studies leading to this thesis. Thank you for sharing your valuable life perceptions; I am forever grateful for your wisdom; I carry it with me daily.

I would like to acknowledge the funding sources that have supported me during my doctoral studies: The Fonds de recherche du Québec – Santé (doctoral training program) and the Natural Sciences and Engineering Research Council of Canada (Alexander Graham Bell Canada Graduate Scholarship).

Thank you to Garo Hakimian, the talented artist who painted the cover of this book.

I want to express my deepest gratitude to Jessifée for being by my side, for the unconditional love, endless support and for bringing so much joy and humility into my life.

I would like to thank Chris and Harry for their friendship and guidance that helped shape my growth both professionally and personally.

This thesis is dedicated to my family. To my uncle Raffi, you will be missed and never forgotten. To my best friends and siblings Alex and Sarine, thank you for being lifelong companions. To my mother, thank you for the countless sacrifices and endless love, and, last, to my role model, my greatest friend, and my biggest source of inspiration, my father, I hope you're as proud of me as I am of you.

Contribution to Original Knowledge

The research projects leading to scientific publications discussed in this thesis provide original contributions to knowledge with regard to innovations of surgeries and post-operative outcomes of bone anchored hearing implants.

Chapter 3 start with a systematic review that most accurately underlines the extrusion rates of bone anchored hearing implants and enumerates reasons behind these losses. Previous research addressing this issue is presented in single cohort studies. To our knowledge, we are the first to evaluate biological and mechanical skull characteristics in cadavers to delineate further on the reasons behind implant extrusions. Concordant to other authors, we present a novel tool to help clinicians determine the integrity of the bone. However, we are the first to correlate the findings of this to established bio-mechanical testing modalities in order to highlight what exactly is the tool measuring. These cadaveric outcomes add important knowledge to the field since these experiments are not possible to do in clinical settings.

The studies described in chapter 4 are important additions to the auditory implant surgery community. The outcomes solidify the existing knowledge that skin thinning (or reduction) during bone anchored hearing implant surgery is unnecessary. Since its publication, the study is frequently cited, and more implant centers across the world have adopted for skin preservation. Moreover, the chapter compares clinical and surgical outcomes of two commonly performed approaches to bone anchored hearing implant placement. The rapidly evolving field of bone anchored hearing implant warrants comparative studies of the sort so that implant centers and manufacturers consider the benefits and disadvantages of each surgical techniques.

One of the most ground-breaking innovations in the field of auditory implants using bone conduction to rehabilitate hearing-impaired individuals is the advent of transcutaneous systems.

Chapter 5 delineated the outcomes in a thorough review of a new transcutaneous system. Many clinics around the world are considering transcutaneous systems, however some reluctance exits considering its surgical approach and its functional auditory gain. The chapter and the thesis addresses these.

Contribution of Authors

Chapter 3. Implant loss, stability and osseointegration

3.1 Factors associated with implant loss

Bezdjian A, Smith RA, Willie B, Thomeer H, Daniel SJ (2018) A systematic review on factors associated with percutaneous bone anchored hearing implant loss. Otology Neurotology. 39(10):e897-e906. [Paper I]

- *Conceptualization and design of the systematic review*: Aren Bezdjian

- *Execution of the systematic review, gathering and tabulating of outcomes, analysis of gathered outcomes*: Aren Bezdjian, Rachel Ann Smith

- *Interpretation of findings, drafting and revisions of the manuscript*: Aren Bezdjian, Bettina Willie, Hans Thomeer, Sam J. Daniel

3.2 ISQ in predicting processor coupling time

Bezdjian A, Smith RA, Bianchi M, Willie BM, Daniel SJ (2020) Intra-operative resonance frequency analysis determines processor coupling time in pediatric and adult bone-anchored hearing implant recipients. [Paper II]

- *Conceptualization and design of clinical study*: Aren Bezdjian, Sam J. Daniel

- *Gathering and tabulating of outcomes, analysis of gathered outcomes*: Aren Bezdjian, Rachel Ann Smith, Marco Bianchi

- *Interpretation of findings, drafting and revisions of the manuscript*: Aren Bezdjian, Bettina Willie, Sam J. Daniel

3.3 Human cadaveric bone characterization with respect to BAHI placement

Bezdjian A, Bouchard A, Rummler M, Zimmermann E, Daniel SJ, Willie B (2020) Age-related changes in temporoparietal bone material properties influence stability of bone-anchored hearing implants. [Paper III]

- *Conceptualization and design of study*: Aren Bezdjian, Bettina Willie
- *Preperation of samples and implantation*: Aren Bezdjian
- *Fracture toughness mechanical testing*: Elizabeth Zimmermann
- *Micro-CT, reconstruction and analysis of images*: Aren Bezdjian, Max Rummler, Alice Bouchard
- *Interpretation of findings, drafting and revisions of the manuscript*: Aren Bezdjian, Bettina Willie, Sam J. Daniel

3.4 Smoking affects stability

Bezdjian A, Verzani Z, Thomeer H, Willie B, Daniel SJ (2020) Smoking as a risk factor for spontaneous bone anchored hearing implant extrusion: A case report and review of literature. Otolaryngology Case Reports. 14:100140. [Paper IV]

- *Conceptualization and design of clinical study*: Aren Bezdjian
- *Case* report: Aren Bezdjian, Hans Thomeer
- Execution *of the systematic review, gathering and tabulating of outcomes, analysis of gathered outcomes*: Aren Bezdjian, Zoe Verzani
- *Interpretation of findings, drafting and revisions of the manuscript*: Aren Bezdjian, Hans Thomeer, Bettina Willie, Sam J. Daniel

Chapter 4. Innovation of outcomes and surgical approaches

4.1 Skin preservation versus reduction

Verheij E, **Bezdjian A**, Grolman W, Thomeer H (2016) Systematic review on complications of non-skin thinning surgical technique in percutaneous bone conduction hearing devices. Otology Neurotology. 37(7):829-37. [Paper V]

- *Conceptualization and design of the systematic review*: Aren Bezdjian, Emmy Verheij, Wilko Grolman
- *Execution of the systematic review, gathering and tabulating of outcomes, analysis of gathered outcomes*: Aren Bezdjian, Emmy Verheij
- *Interpretation of findings, drafting and revisions of the manuscript*: Aren Bezdjian, Emmy Verheij, Hans Thomeer

4.2 Response to a letter

Verheij E, **Bezdjian A**, Grolman W, Thomeer HGXM (2017) Response to comment on "a Systematic Review on Complications of Tissue Preservation Surgical Techniques in Percutaneous Bone Conduction Hearing Devices" Otology Neurotology. 38(1):158-159. [Paper VI]

- *Conceptualization and drafting of the letter*: All authors

4.3 Comparing two surgical approaches

Bezdjian A, Smith RA, Yuang L, Gabra N, Bianchi M, Daniel SJ (2019) Experience with minimally invasive Ponto surgery and linear incision approach for pediatric and adult bone anchored hearing implants. Annals of Otology, Rhinology & Laryngology. 3489419891451. [Paper VII]

- *Conceptualization and design of clinical study*: Aren Bezdjian, Sam J. Daniel

- *Gathering and tabulating of outcomes, analysis of gathered outcomes*: Aren Bezdjian, Rachel Ann Smith, Luhe Yuang, Nathalie Gabra, Marco Bianchi

- *Interpretation of findings, drafting and revisions of the manuscript*: Aren Bezdjian, Sam J. Daniel

4.4 Skin tolerability evaluation scales

Bezdjian A, Nathoo-Khedri N, Bianchi M, Strijbos R, Sewitch M, Thomeer H, Daniel SJ (2020) An inter-variability study assessing skin tolerability of percutaneous bone anchored hearing implants using the Holger's classification, the IPS, and Tullamore scales. Otology Neurotology. (revisions submitted). [Paper VIII]

- *Conceptualization and design of study*: Aren Bezdjian

- *Gathering and tabulating of outcomes, analysis of gathered outcomes*: Aren Bezdjian, Nabil Nathoo-Khedri, Ruben Stijbos

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4.5 Worn out screw technical note

Schwarz Y, Bianchi M, **Bezdjian A**, Daniel SJ (2017) Strategies for removing a worn-out Bone Anchored Hearing Aid screw. Clinical Otolaryngology. 43(2):782-783. [Paper IX]

- *Conceptualization and design of study*: Yehuda Schwarz, Aren Bezdjian

- *Gathering outcomes, literature search and creation of algorithm*: Yehuda Schwarz, Aren Bezdjian

- *Drafting and revisions of the manuscript*: Yehuda Schwarz, Aren Bezdjian, Marco Bianchi, Sam J. Daniel

Chapter 5. Exploring transcutaneous systems

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Bezdjian A, Bruijnzeel H, Thomeer H, Grolman W (2017) Audiologic and peri-operative outcomes of the Sophono^{TM} transcutaneous bone conduction hearing device: A systematic review. International Journal of Pediatric Otorhinolaryngology. 101:196-203. [Paper X]

- *Conceptualization and design of the systematic review*: Aren Bezdjian, Wilko Grolman

- *Execution of the systematic review, gathering and tabulating of outcomes, analysis of gathered outcomes*: Aren Bezdjian, Hanneke Bruijnzeel

- *Interpretation of findings, drafting and revisions of the manuscript*: Aren Bezdjian, Hans Thomeer

5.2 Auditory gain from bone conduction hearing devices

Bezdjian A, Bruijnzeel H, Daniel SJ, Thomeer HGXM (2018) Response to "How to quantify the 'auditory gain' of a bone-conduction device; comment to the systematic review by Bezdjian et al." International Journal of Pediatric Otorhinolaryngology. 109:188-189. [Paper XI]

- *Conceptualization and drafting of the letter*: All authors

List of papers included in thesis

This thesis includes the following scientific articles:

1. **Bezdjian A**, Smith RA, Willie B, Thomeer H, Daniel SJ (2018) A systematic review on factors associated with percutaneous bone anchored hearing implant loss. Otology Neurotology. 39(10):e897-e906. [Paper I]

2. **Bezdjian A**, Smith RA, Bianchi M, Willie BM, Daniel SJ (2020) Intra-operative resonance frequency analysis determines processor coupling time in pediatric and adult bone-anchored hearing implant recipients. [Paper II]

3. **Bezdjian A**, Bouchard A, Rummler M, Zimmermann E, Willie B, Daniel SJ (2020) Age-related changes in temporoparietal bone material properties influence stability of bone-anchored hearing implants. [Paper III]

4. **Bezdjian A**, Verzani Z, Thomeer H, Willie B, Daniel SJ (2020) Smoking as a risk factor for spontaneous bone anchored hearing implant extrusion: A case report and review of literature. Otolaryngology Case Reports. 14:100140. [Paper IV]

5. Verheij E, **Bezdjian A**, Grolman W, Thomeer H (2016) Systematic review on complications of non-skin thinning surgical technique in percutaneous bone conduction hearing devices. Otology Neurotology. 37(7):829-37. [Paper V]

6. Verheij E, **Bezdjian A**, Grolman W, Thomeer HGXM (2017) Response to comment on "a Systematic Review on Complications of Tissue Preservation Surgical Techniques in Percutaneous Bone Conduction Hearing Devices" Otology Neurotology. 38(1):158-159. [Paper VI]

7. **Bezdjian A**, Smith RA, Yuang L, Gabra N, Bianchi M, Daniel SJ (2019) Experience with minimally invasive Ponto surgery and linear incision approach for pediatric and

adult bone anchored hearing implants. Annals of Otology, Rhinology & Laryngology. 3489419891451. [Paper VII]

8. **Bezdjian A**, Nathoo-Khedri N, Bianchi M, Sewitch M, Daniel SJ (2020) An inter-variability study assessing skin tolerability of percutaneous bone anchored hearing implants using the Holger's classification, the IPS, and Tullamore scales. Otology Neurotology. (revisions submitted). [Paper VIII]
9. Schwarz Y, Bianchi M, **Bezdjian A**, Daniel SJ (2017) Strategies for removing a worn-out Bone Anchored Hearing Aid screw. Clinical Otolaryngology. 43(2):782-783. [Paper IX]
10. **Bezdjian A**, Bruijnzeel H, Thomeer H, Grolman W (2017) Audiologic and peri-operative outcomes of the Sophono^{TM} transcutaneous bone conduction hearing device: A systematic review. International Journal of Pediatric Otorhinolaryngology. 101:196-203. [Paper X]
11. **Bezdjian A**, Bruijnzeel H, Daniel SJ, Thomeer HGXM (2018) Response to "How to quantify the 'auditory gain' of a bone-conduction device; comment to the systematic review by Bezdjian et al." International Journal of Pediatric Otorhinolaryngology. 109:188-189. [Paper XI]

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List of Abbreviations

ACU, acute care unit

BAHA, bone anchored hearing aid

BAHI, bone anchored hearing implant

BCHD, bone conduction hearing device

CAD, coronary artery disease

CHL, conductive hearing loss

COM, chronic otitis media

COPD, chronic obstructive pulmonary disease

dB, decibels

GCBI, Glasgow children's benefit inventory

H, hours

HL, hearing loss

Hz, hertz

IRC, insuffisance renale chronique

ISQ, implant stability quotient,

m, months

Mins, minutes

MIPS, minimally invasive Ponto surgery

N, number

N/A, not available

NS, not specified

OCA, ossicular chain anomaly

PTA BC bone conduction pure tone average thresholds

PTA, pure tone average

RFA, resonance frequency analysis

RMS, root-mean-square

SD, standard deviation

SEE, standard errors of the estimates

SNHL, sensorineural hearing loss

SRT, speech reception threshold

SS, single-sided

TIPI, Italian adaptation of the Northwestern University Children's Perception of Speech Instrument

WRS, word recognition score

voi, volumes of interest

yo, years old.

Chapter 1

Introduction

1.1 Principles of the Auditory System

The auditory system is the sensory system for hearing. Hearing in humans plays a central role in the way we interact with our environment. It is necessary for social communication through sound detection, localisation and discrimination of location, pitch, loudness and quality, and also serves as a warning and orientation system in spatial directions. The auditory system includes both the sensory organs and the auditory parts of the nervous system. It is broadly divided into two parts: the peripheral auditory system and the central auditory system. The peripheral system includes the external, middle and inner ear, while the central system comprises the auditory brainstem (cochlear nuclei, trapezoid body, superior olivary complex and lateral lemniscus), the midbrain (the inferior colliculi), the thalamus (the medial geniculate nucleus) and the auditory part of the cerebral cortex.

1.1.1 Anatomy of the ear

The various features of the peripheral auditory system permitting sound to travel through the system is illustrated in Figure 1. The principle function of this auditory system is to convert acoustic energy into neural stimuli, which are then transmitted to the brain for processing.

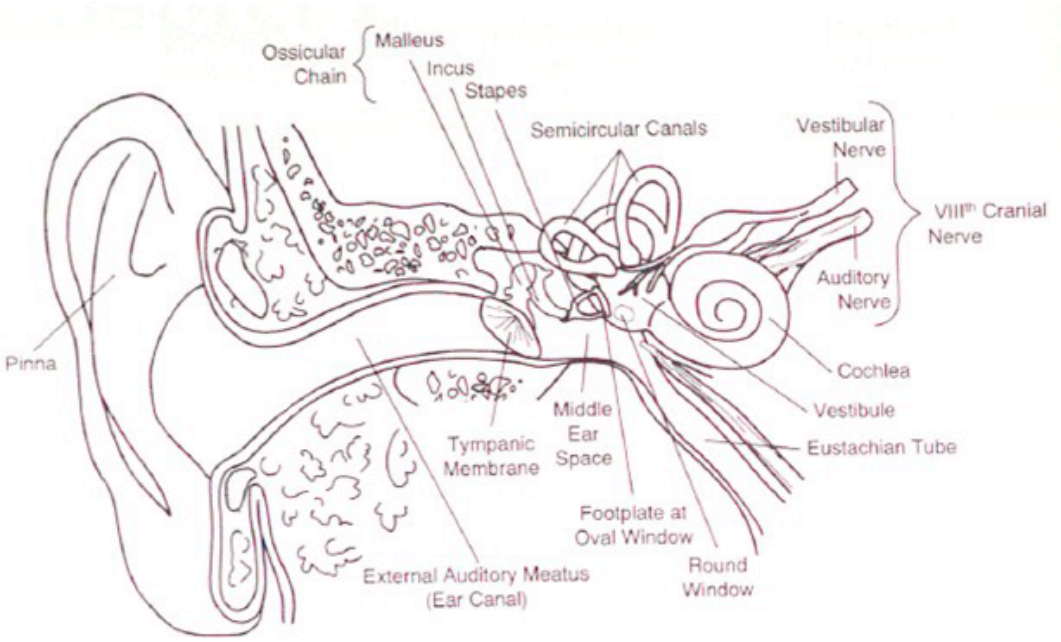

Figure 1. Diagram of the human peripheral auditory system. Adapted from Gelfand (2009).

The external ear of the peripheral auditory system commences with the pinna or auricle with a distinct shape that allows collect air vibrations. It is comprised of a thin plate of elastic cartilage covered by skin. It possesses both extrinsic and intrinsic muscles, which are directly connected to the facial nerve. The external auditory meatus is a curved tunnel-like structure that permits sound to travel connecting the auricle to the tympanic membrane (TM).

The middle ear is essentially and air-filled space in the temporal bone between the TM and the internal ear structures. This space communicates with the eustachian tube; a canal that connects the middle ear to the nasopharynx, which consists of the upper throat and the back of the nasal cavity. It controls the pressure within the middle ear. The three smallest bones of the human body are found in the middle ear. They are called auditory ossicles and they receive mechanical information from the sound waves hitting the TM. This initiates an ossicular chain movement starting from the malleus (hammer), then incus (anvil) and last, stapes (stirrup) (Figure 2). The TM

and the ossicles act as a transducer, changing the energy form of the mechanical sound arriving from the external auditory meatus.

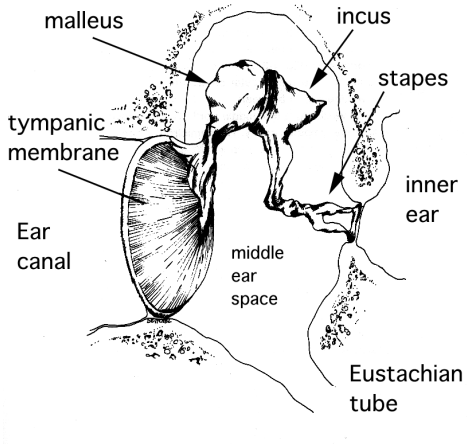

Figure 2. Middle ear showing the tympanic membrane and ossicles (Healthfavo, 2014).

The inner ear is a fluid filled area that is the final step in converting sound waves gather from the external ear and travelled to the middle ear to neural stimulation to be sent to the auditory brain via the auditory nerve. This part of the peripheral auditory system is also responsible for the body's balance mechanism (vestibular system). It contains the primary hearing structure called the cochlea. The cochlea consists of three fluid-filled sections coiled in two and a half turns. The inner duct containing the sensory epithelium is also referred to as the scala media. This later divides the outer duct into the scala vestibuli superiorly and scala tympani inferiorly (Salvi et al., 2007) (Figure 3). Sound energy enters the cochlea via the stapes bone at the oval window. The scala vestibuli in the basal end of the oval window is the place where the sound-induced vibrations are transmitted to the cochlear fluids. This creates a motion in the basilar membrane, creating a traveling wave that goes from the base of the cochlea to the apex. Each location on the basilar membrane is tuned to a specific frequency. Low frequency stimuli cause more vibration at the apex, while high-

frequency stimuli cause more vibration at the base of the basilar membrane. This tonotopy is maintained throughout the auditory pathway (Hudspeth, 1989).

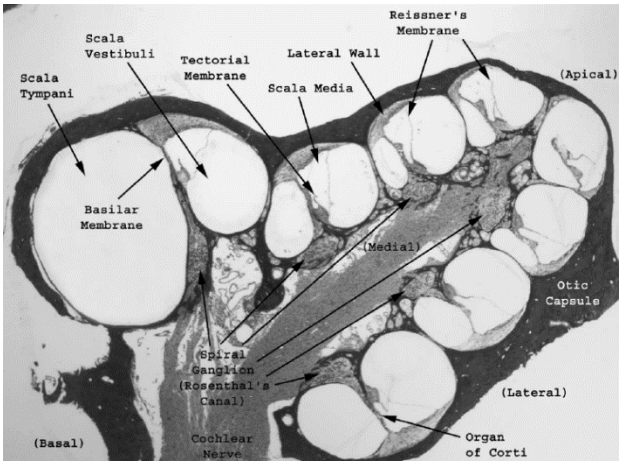

Figure 3. Light micrograph of a cross-section of the guinea pig cochlea (Raphael & Altschuler, 2003).

Auditory hair cells are classified into two categories; inner hair cells (IHC) arranged as a single row medially and three rows of outer hair cells (OHC) laterally as seen in Figure 4. They are called hair cells because they have tufts of stereocilia (also called hair bundles) projecting from their surfaces. Furthermore, a thin membrane attached over the stereocilia of the hair cells called tectorial membrane follows the movement after the sound-induced vibrations reach the cochlea (Salvi et al., 2007). This arrangement allows the proper transmission of mechanical energy to hair cells with every acoustically transmitted vibration into the cochlear fluids.

The auditory hair cells located in the organ of Corti act as transducers through their stereocilia, converting the sound-induced vibrations into electrical activity. The mechanical process of the basilar membrane creates a force in the stereocilia of auditory hair cells that allows the opening of sensitive mechanoelectrical transduction channels. This, in turn, promotes depolarization of spiral ganglion neurons (SGN) through the opening of potassium channels

(Hudspeth, 1989, 1992). This change in the resting membrane potential forms a synapse with a dendrite from a SGN. The axons of the SGNs form the auditory nerve, which exits the cochlea and temporal bone through the internal auditory meatus, transmitting neural stimuli to the auditory cortex of the brain. Finally, there, at the neural level, the stimuli are processed into sound (Bess & Humes, 2008; Gelfand, 2009).

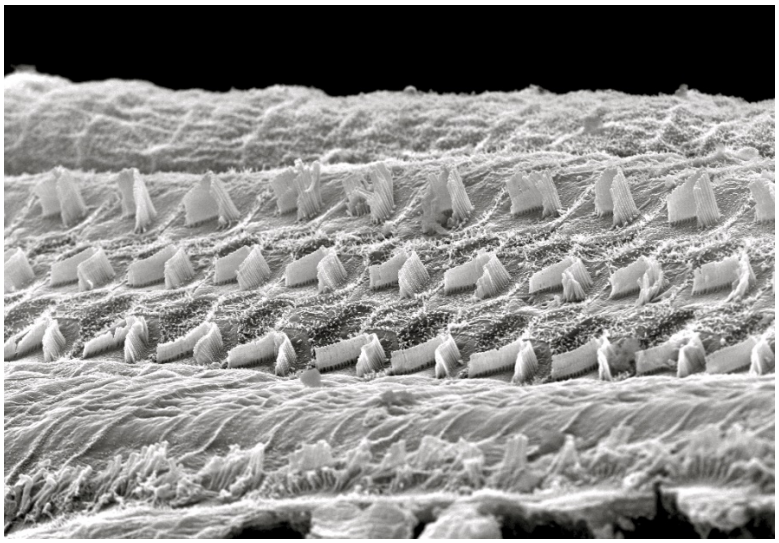

Figure 4. Inner hair cells (IHC) arranged as a single row of inner hair cells medially and three rows of outer hair cells (OHC) laterally in a guinea pig (Property of McGill Auditory Sciences Laboratory, 2018, printed with permission).

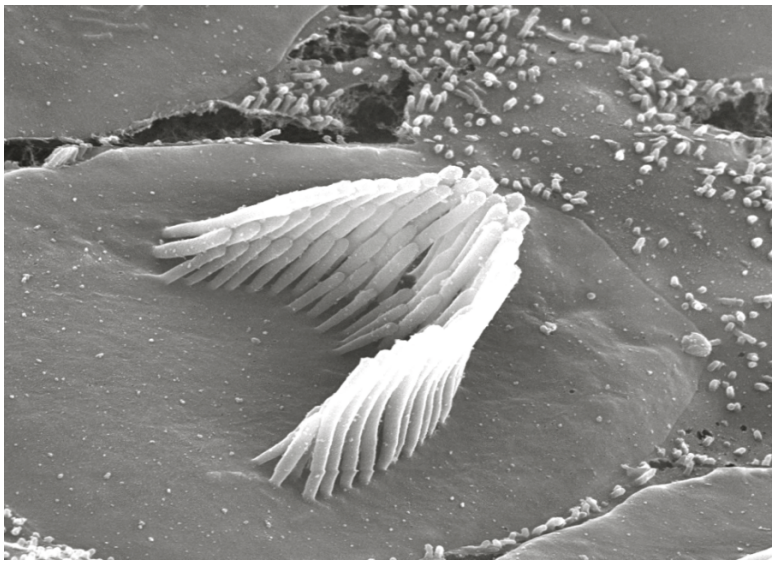

Figure 5. A SEM image of a single auditory hair cell of a guinea pig (Property of McGill Auditory Sciences Laboratory, 2018, printed with permission).

While the auditory hair cells (Figure 6) in the cochlea are the main signal transducers for sound stimuli, the central auditory pathway integrates the information to elicit a response to sounds. Figure 6 shows the neuroanatomical pathways in the central auditory system, which begins with the brainstem at the cochlear nucleus where the auditory nerve fibres travelling from the cochlea terminate (Musiek et al., 2007). Neurons of the auditory nerve make the first synaptic connection at the cochlear nucleus located in the dorsolateral side of the brainstem. The axons of neurons from the cochlear nuclei proceed to the superior olivary nuclei complex in the medulla. The neuronal axons proceed to the inferior colliculus in the midbrain, which contains neurons with sharply defined frequency sensitivity, similarly to the cochlea (Aitkin et al., 1975). The outputs are then sent to the medial geniculate body also referred to as the auditory thalamus from where they are finally sent to the auditory cortex (Musiek et al., 2007). Central auditor pathways involve all ascending and descending neuronal projections interconnecting the auditory nerve, brainstem, midbrain, thalamus, and cerebral cortex.

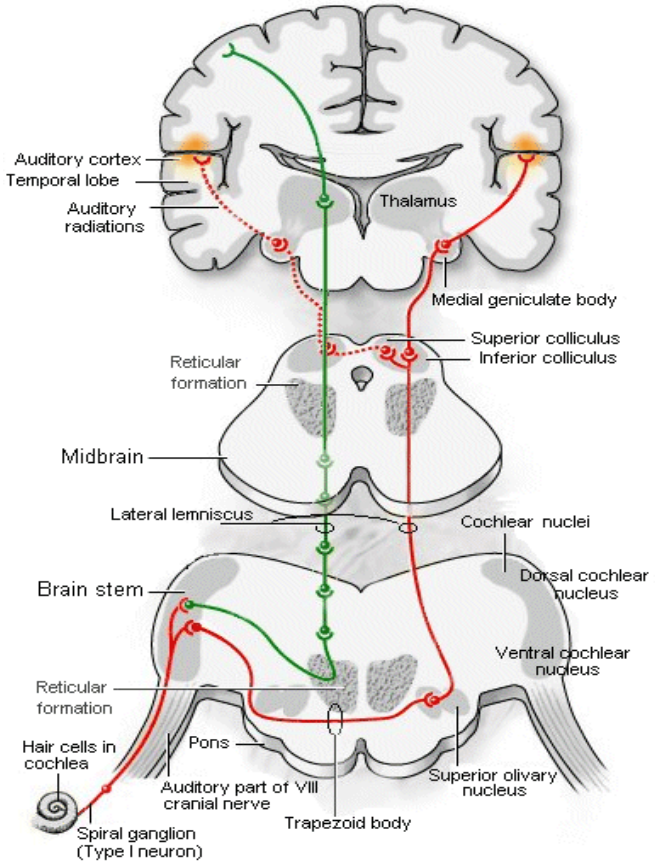

Figure 6. Neuroanatomical pathways in the central auditory system. Illustration of the major central ascending auditory pathways for sound entering via the right cochlea. Commissural pathways and descending feedback projections from higher centers (FirstYears, n.d.).

1.1.2 Hearing

The human species has an auditory system that allows for the detection of sounds in the frequencies ranging from 20 to 20000 Hz with a greatest sensitivity for the 500 to 4000 Hz range. This corresponds to the frequencies for the understanding of human speech (Jahn & Santo-Sacchi, 2001). The perception of a frequency is commonly referred to as the pitch of a sound. A high pitch sound corresponds to a high frequency sound wave; and vice versa. The auditory system is tonotopically organized; meaning that each frequency is thoroughly organized within all of the

structures of the auditory system, starting at the cochlear level and along the auditory pathway, to the auditory cortex (Bear et al., 2007; Mann & Kelley, 2011).

For sounds to be perceived by the human auditory system, a certain sound intensity is required. Sound intensity is defined as the power exerted by sound waves per unit area. More simply, this refers to the volume of sound. This amplitude of sound waves is derived from the pressure changes occurring at the TM. The decibel scale is used to quantify intensity, loudness, or sound level. The intensity of a sound in bels is the logarithm of the ratio of the intensity of that sound and a standard sound. A decibel (dB) is 0.1 bel.

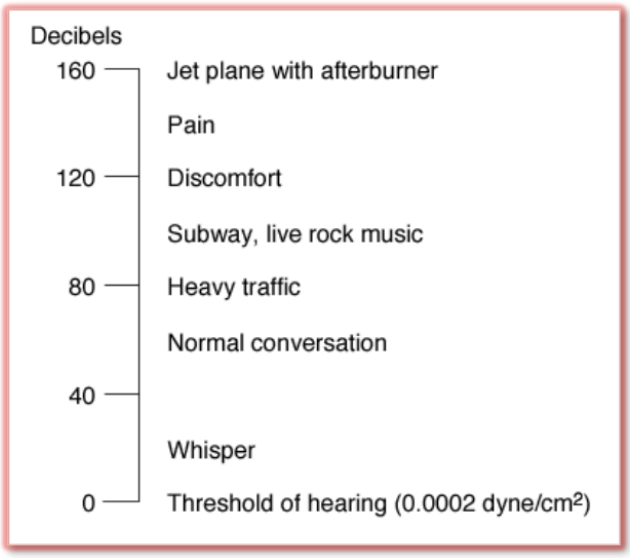

Figure 7. Decibel scale for common sounds (Almukhtar, 2018)

Hearing is permitted due to two pathways allowing sound to be transferred to the primary hearing structure; the cochlea. Air conduction hearing occurs via the transmission of sound vibrations to the eardrum through the external auditory meatus as previously stated. However, there is a secondary hearing pathway called the bone conduction pathways defined by the transmission of sound vibrations to the internal ear through the cranial bones, therefore bypassing the middle and external ears. This will be further discussed in chapter 1.4.

1.1.3 Hearing loss

Hearing loss is defined as the reduced ability to hear sounds. It can occur at any age, have many causes, and be gradual or sudden. Therefore, the part of the auditory system involved determines the type of hearing loss. Depending on the cause, hearing loss can be mild or severe, temporary or permanent (Figure 8).

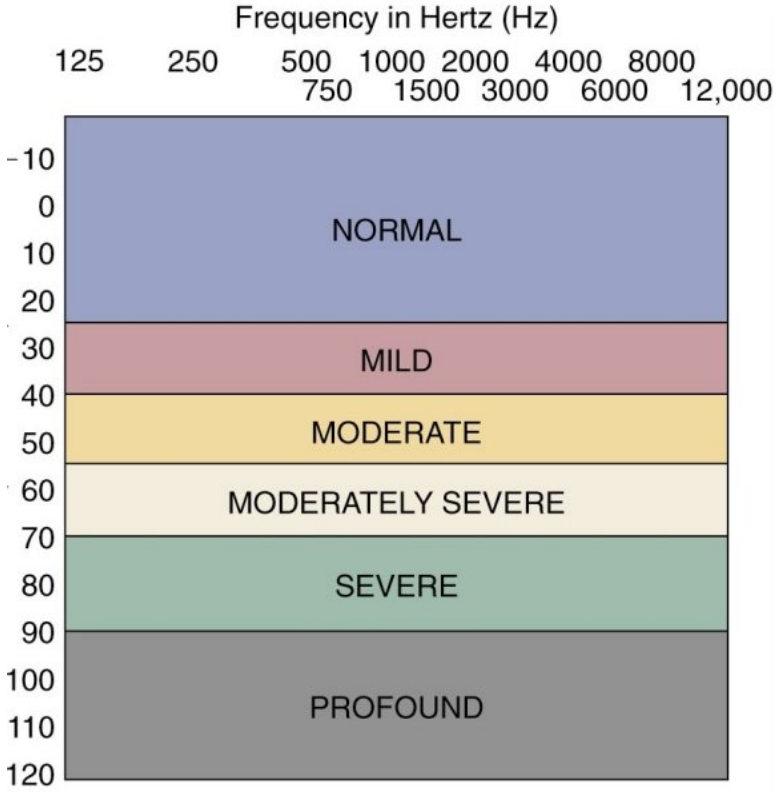

Figure 8. Graphic representation of categories of hearing loss (Marieb et al. 2008).

Hearing loss is classified into three types: conductive, sensorineural, and mixed hearing loss. Conductive hearing loss results from impedance from the outer and/or middle ear. Therefore, conditions preventing the sound traveling from reaching the inner ear is considered a cause of conductive hearing loss. Common examples are otitis, earwax impaction, TM perforations or damage, and otosclerosis (Paul & Whitelaw, 2010). Sensorineural hearing loss occurs when the hearing loss is a result of shortcomings in the inner ear or the auditory nerve. Sensorineural hearing

loss encompasses the sensory component (cochlear function) and the neural component (auditory nerve). In rare occurrences where deafness results from cortical damage, it is also considered a type of sensorineural hearing loss. Central auditory disorder results from problems in the processing of sound in higher auditory areas of the brain. This type of auditory deficiency affects more complex auditory processes such as understanding speech when there is background noise. Lastly, mixed hearing loss is a combination of conductive and sensorineural hearing loss.

Hearing loss is a prevalent condition that impacts 466 million people worldwide (5% of the world's population), and 34 million of these are children (WHO, 2020). Hearing loss impacts quality of life. Its severity is dependent on the type and degree of hearing loss. To determine these, clinical hearing tests, called audiometry, is performed. Pure tone audiometry is a subjective test in which a person responds to sound stimuli of varying frequencies (pitch) and intensities (loudness). This, it requires a cooperation, therefore presenting challenges for toddlers and young children. The hearing sensitivities at each frequency (usually tested from 250 to 8000 Hz) are plotted on a chart known as an audiogram (Figure 9).

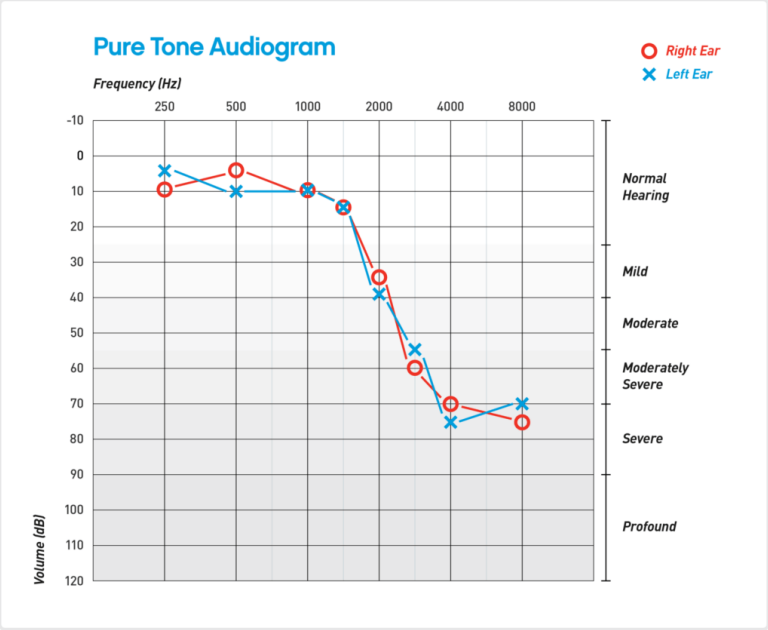

Figure 9. Example of a pure-tone audiogram symbols dip from 2000-8000 Hz, which indicates a high-frequency hearing loss that is mild-to-severe. This person would you trouble hearing high-pitched sounds such as birds singing and certain words (Botella, n.d.).

To differentiate conductive from sensorineural hearing loss, bone conduction testing is conducted. Bone conduction audiometry measures pure-tone thresholds using a mechanical device that transmits sounds via vibration through the forehead or mastoid bone while masking the tested ears to eliminate air conduction hearing (Katz & Lezynski, 2002).

1.2 Bone

Bone is a living organ consisting of bony tissue taking various forms. It is a complex, vascularised, cellular and highly mineralised connective tissue. Bone tissue is created, maintained and resorbed by different cells around and within the bone matrix. Its primary functions are to provide mechanical support and framework to the human body, allow locomotion, anchor muscles of the body, protect vital organs, and serve as a metabolic mineral reservoir (Burr, 2019). Bone is a dynamic organ made up of an extracellular matrix that undergoes several turnovers compared to

other organs of the mammalian body. This mineral and matrix are undergoing continuous changes to allows regeneration, repair and adaptation of bone in consequence to its changing environment. Intercellular signalling, between the osteoprogenitor cells and mature bone cells, regulates and balances activities of bone cells during bone remodelling and bone growth (Bayliss et al., 2012). In fact, one tenth of the total bone volume undergoes remodelling every year. Three distinct mature bone cells are involved in this regulatory process: osteoblasts, osteocytes and osteoclasts. The coordinated activities of osteoclasts and osteoblasts are essential for maintaining bone structure. Bone is formed by osteoblasts which are derived from pluripotent mesenchymal stem cells. Their primary function is the synthesis and mineralisation of osteoid and organic matrix. They secrete macromolecules which make up the extracellular matrix. The abundant type 1 collagen is the principal component of bone which provides resistance to tensile forces. The second main component of the matrix is calcium phosphate that adds compressive strength to the overall bone framework (Buckwalter et al., 1996). In contrast to osteoblasts, osteoclasts, bone-resorbing cells, are large, multinucleated cells derived from the monocyte/macrophage lineage. Their function, vital for bone modeling and remodeling, is to act in the degradations of bone matrix and mineral during bone resorption. Osteocytes are found in lacunae. Via the cytoplasmic extensions running through the canalicular network, these cells are interconnected. They interact with neighbouring cells via their dendrites which pass through small channels called canaliculi (Bellido et al., 2019). Osteocytes act as sensors and convert stimuli of mechanical loading into biochemical signals (Bayliss et al., 2012). They do so by coordinating their function in response to the environmental cues it detects such as mechanical stress or hormonal signals.

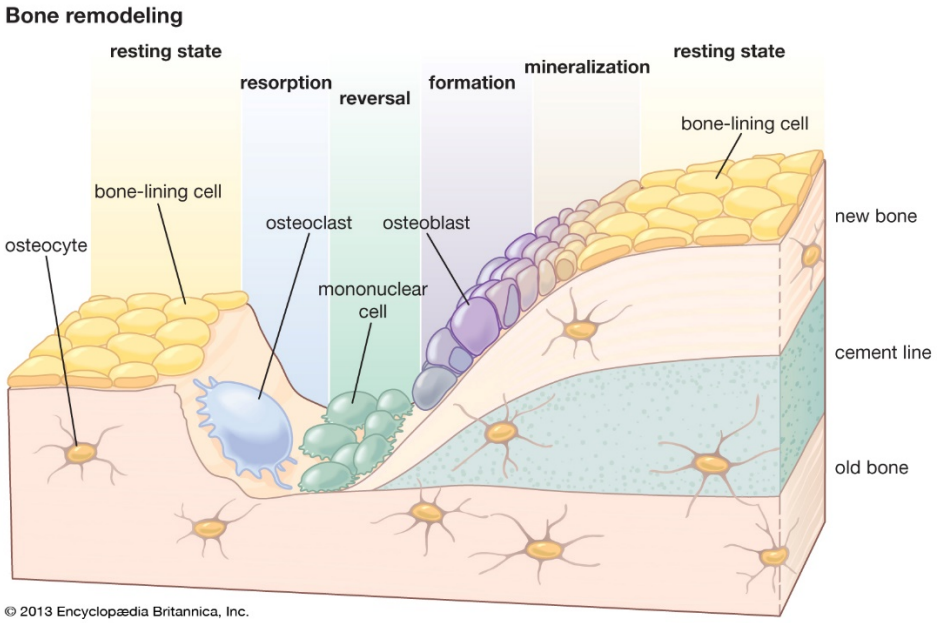

Figure 10. Bone remodeling, where formation and resorption are coupled. After an activation signal, osteoclasts are recruited, to resorb old bone, followed by osteoblasts laying down osteoid, which mineralizes into new bone (Britannica, 2013).

Morphologically, bone is divided into two types: cortical and trabecular bone. Cortical bone is compact and forms the hard outer layer of bones while the trabecular bone is spongy in structure and makes up the inner layers of the bones of the human body. Bone can also be classified as long bone (i.e. tibia, femur) or flat bone (i.e. skull) or irregular bone (i.e. hip). The internal and external surfaces are lined with cellular layers called endosteum and periosteum respectively (Bellido et al., 2019).

1.2.1 Temporoparietal skull bone

The skull is a bony structure that supports the face and forms a protective cavity for the brain. It is comprised of many bones, which are formed by intramembranous ossification, and joined by sutures (fibrous joints). The bones of the skull can be categorized as two groups: bones of the cranium (cranial roof and cranial base) and bones of the face.

The temporal bone contributes to the lower lateral walls of the skull. It contains the middle and inner portions of the ear and is crossed by the majority of the cranial nerves. The lower portion of the bone articulates with the mandible, forming the temporomandibular joint of the jaw. In the cranial bones, two layers of compact cortical tissue known as the tables of the skull. The intervening cancellous tissue is called the diploë. The diploë is a trabecular part, spongy cancellous bone, separating the inner and outer layers of the cortical bone of the skull (Figure 11).

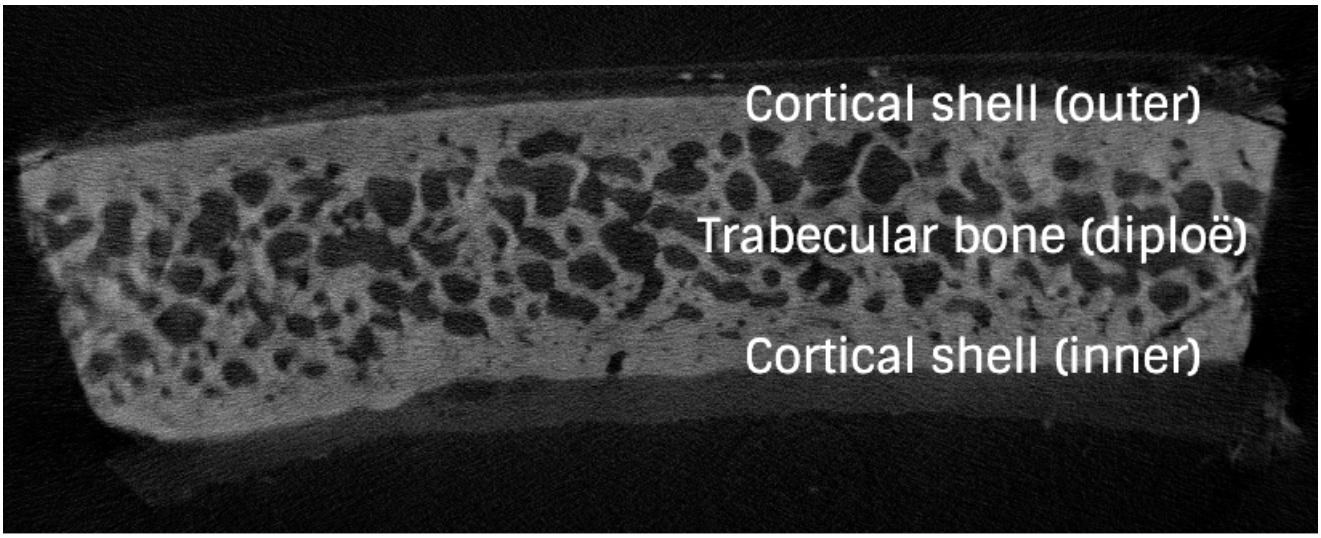

Figure 11. Micro-CT image displaying the skull bone where two layers of cortical shells encompass a trabecular part termed diploë

Current recommendations for the location of the osseointegrated bone anchored hearing implant, recommend for placement approximately 5 to 7 cm posterosuperior to the external auditory canal (EAC) (Figure 12). This allows for a margin of safety to avoid the auricle, as well as the sigmoid sinus, when placing the implant in the calvarium. One of the major concerns with implanting BAHIs is the thickness of the temporal bone at the implant site (Papsin et al., 1997). It is uncommon to perform CT scans of an individual to determine skull thickness prior to

implantation. Thus, little is known concerning how skull thickness varies with age or co-morbidity at the implantation site and over-drilling can occur in rare cases.

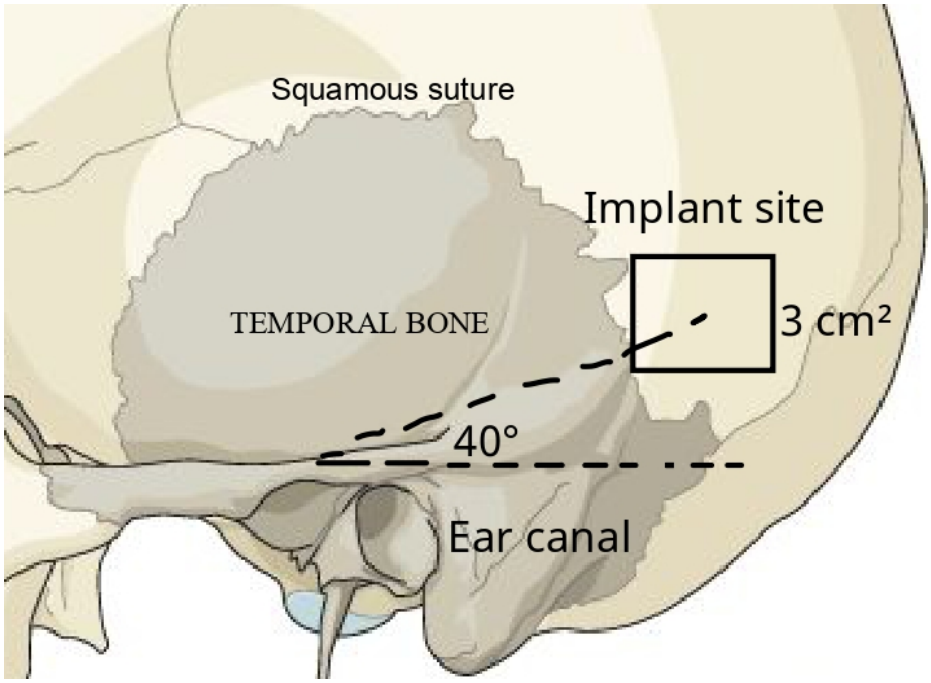

Figure 12. Illustration of the location of the bone anchored hearing implant on the temporoparietal skull bone

1.2.2 Osseointegration

Osseointegration is a bone healing behaviour when it adapts to an implant. It's a biological process termed to identify the dynamic functional and structural anchorage of the bone to a prosthetic by the formation of bone tissue around the implant (Brånemark et al., 1977). Most of what is known about tissue penetrating bone-implant osseointegration comes from dental implants pioneered by Brånemark in the 60's (Albrektsson et al., 1981).

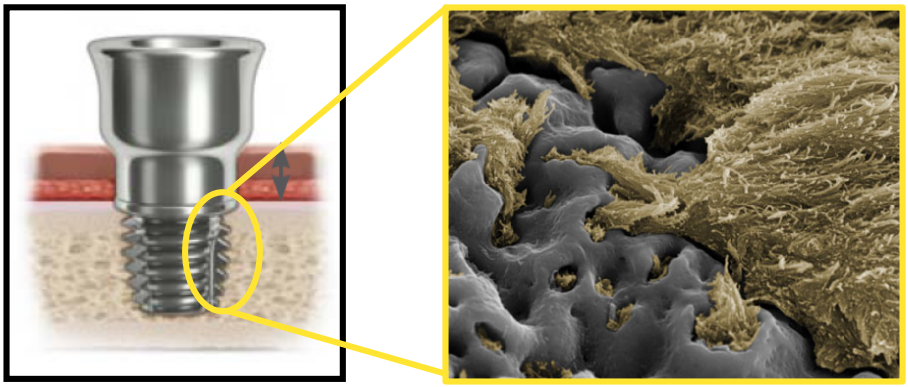

Figure 13. Osseointegration of the bone-implant interface (Westover et al., 2016).

Osseointegration is a process initiated by bone healing where an initial inflammation is followed by bone formation and bone remodeling. Bone healing around implants involves a cascade of cellular events (Figure 14). A rich blood supply near the implant surface is important to support the bone healing processes which allows for the biological fixation of the implant. The cellular events involved in bone healing are as followed: 1) Blood cells activate and release cytokines and other soluble, growth, and differentiation factors to influence clot formation. 2) The formed fibrin matrix acts as a scaffold for the migration and differentiation of osteogenic cells to induce bone healing. 3) A thin layer of calcified and osteoid tissue is deposited by osteoblasts directly on the surface of the implant. 4) This newly calcified matrix and the presence of osteogenic cells induce the formation of new woven and trabecular bone.

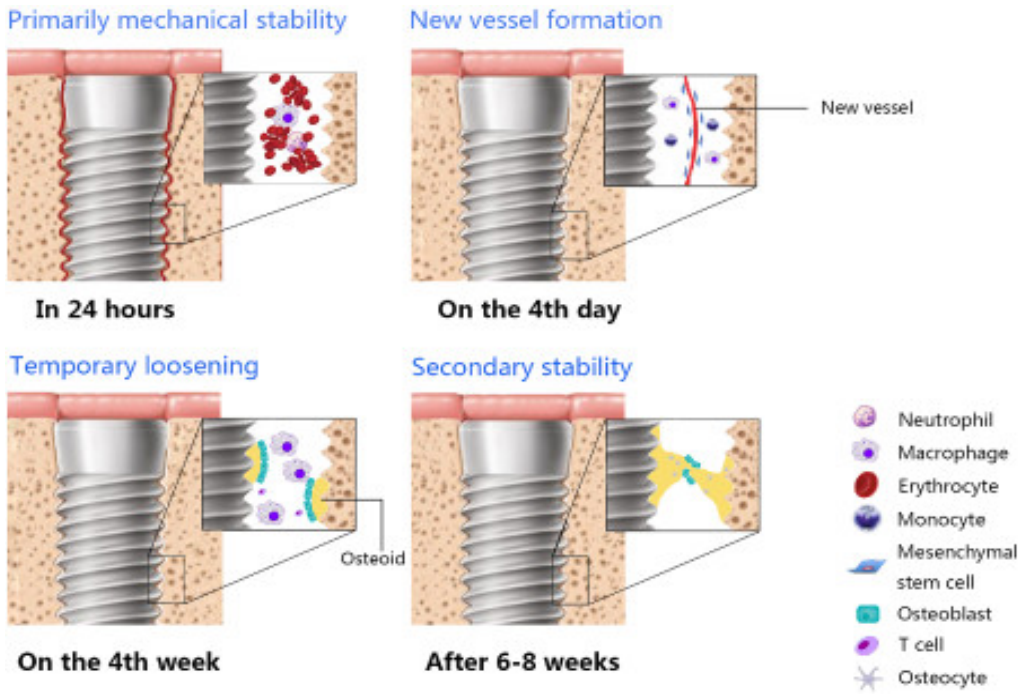

Figure 14. Cellular involvement of bone healing commencing by an inflammatory response to new formed bone stabilising the implant (Mavrogenis et al., 2009)

In sum, there are three phases of osseointegration. The first is the migration of the osteogenic bone cells to the implant surface. The initial inflammatory response occurs within the first 24 hours after implantation and the migration of the bone cells to the implant surface occurs within the first 4 days (Wang et al., 2016). The second phase is new bone formation, which results in a mineralized matrix similar to the cement line in the host bone. New bone formation occurs on the implant surface around days 5 – 7 and by 4 weeks following implantation the new bone on the implant surface has connected to the host bone (Wang et al., 2016). Finally, the third phase of osseointegration involves bone remodeling (Davies, 2003; Ellingsen & Lyngstadaas, 2003) and the end result is a structural integration at the bone-implant interface. After 8 weeks, the bone-implant interface consists of mature lamellar bone in direct contact with the implant surface (Wang et al., 2016).

Loading of bone anchored implants can lead to micromotion at the bone-implant interface that might impede the osseointegration process. The early reports indicate that an immobile healing period of 3 to 6 months is required to limit micromotion during healing and permit osseointegration to occur (Brånemark et al., 1985). Several researchers have shown that micromotion induced by loading can lead to a fibrous encapsulation at the bone-implant interface impeding osseointegration (Cameron et al., 1973; Ducheyne et al., 1977; Schatzker et al., 1975; Szmukler-Moncler et al., 1998; Uhthoff, 1973; Akagawa et al., 1986; Brunski, 1992; Brunski et al., 1979; Lum et al., 1991). Contrarily, other reports with early loading protocols have shown successful osseointegration despite some micromotion during healing (Akagawa et al., 1993; Deporter et al., 1990; Hashimoto et al., 1988; Szmukler-Moncler et al., 1998). It is well-known that several factors such as implant design, surgical approach and patient-related factors are factors that can help to achieve adequate primary stability to prevent excessive micromotion and allow for proper osseointegration (Bezdjian et al., 2018; Szmukler-Moncler et al., 1998).

1.3 Bone conduction hearing

Bone conduction is the principle of sound propagation through bone that results in vibrations traveling and reaching the basilar membrane allowing the perception of hearing. Every person that is not hearing-impaired has this ability to hear through bones. This is the reason why we perceive our own voice differently from a recording than when we listen to ourselves talking during everyday life. This is mainly due to the fact that, when we speak, sound produced by our vocal cords create sound vibrations that travel through the bones of our head (jawbone, calvaria) and is directly sensed by the cochleae rather than through the air around the head to the ears. Bone conduction hearing is better at transmitting low frequencies compared to air conduction hearing. The sound of your voice from a recording entering your auditory brain is through air conduction

hearing. Since you are used to perceiving your own voice through bone conduction hearing, you often perceive your voice on a recording to be higher pitched. An interesting fact: your voice out of a recording is how everyone else hears you and you are the only one that hears the sound of your voice like you do. Next time you are under water try yelling. Since sound does not travel in water, you will only hear through your bones.

Bone conducted sound transfer is used in several fields. The military was one of the first adopters of bone conduction hearing in their helmets for example. This permit soldiers to hear using both sound conduction pathways and not be acoustically disconnected from their surroundings on the battlefield (via air conduction) while communicating with their peers and command centers (via bone conduction). Similarly, to utilize both sound conduction pathways in our everyday life, bone conduction headphones are becoming increasingly popular. This allows, for example, listening to music while cycling or running on the streets without being disconnect from the proximity acoustic world, bearing an important safety advantage. Nonetheless, like any technological innovation in society, bone conduction hearing has important risk factors. For example, a German media company called Sky Deutschland has found a new dimension for advertisement targeting train commuters. They integrated bone conduction hearing technology to send audio information (ads) transmitted via the window of the train. Thus, when commuters rest their head against the glass the ads are heard inside their head (Kelion, 2013). The principle of bone conduction hearing is used to rehabilitate hearing impaired individuals with the bone anchored hearing systems.

1.3.1 Bone anchored hearing systems

Conventional hearing aids capture surrounding sounds through a microphone and amplify it to transmit via a small speaker placed in the auditory canal. This is the amplification

and transmission of air conduction. On the other hand, the bone anchored hearing systems utilize the bone conduction hearing pathway by transforming the sounds captured via the microphone to vibrations that are sent through the skull bone (bypassing the external and middle ears) to be sensed by the inner ear (Figure 15).

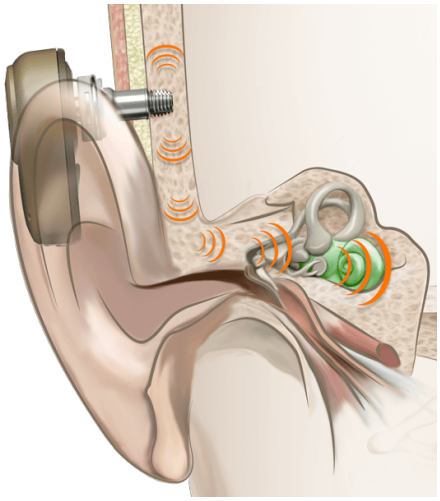

Figure 15. Bone conduction system consisting of a titanium implant placed in the bone behind the ear and a sound processor that attaches to the implant. The sound processor converts sounds into vibrations, which are then sent through your skull bone and directly on to your inner ear (Oticon Medical, n.d.).

The main components of the bone anchored hearing system include a sound processor, a coupling piece, a screw, an abutment and the implant. The implant is placed surgically in the skull bone. An abutment is attached to the implant held in place with a screw. The screw allows post-operative changes of the abutment to occur, if necessary. Then, a sound processor containing a coupling piece is attached to the abutment (Figure 16).

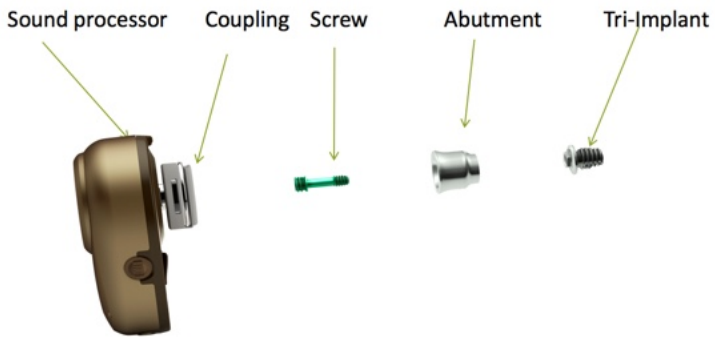

Figure 16. Components of the percutaneous bone anchored hearing implant system (PONTO, Oticon Medical) (Samra, 2018).

Due to the principles of bone conduction hearing, the inner ear must be (near) intact in order for these devices to work, since they rely on sound transmission from the cochlea via the auditory nerve to the auditory system. The hearing loss categorisation rendering hearing-impaired individuals to be candidates of these devices are as followed:

- Conductive hearing loss, the conduction of sound waves is obstructed in the outer ear, or along the auditory canal. There can also be impedance due to a TM or middle ear ossicle issue.
- Mixed hearing loss
- Single sided deafness (SSD), a patient with a normal or close to normal hearing in one ear and profoundly impaired hearing in the contralateral.

Hearing-impaired individuals with these types of hearing loss can benefit from a bone anchored hearing system. These systems were developed and put into clinical use in the late 1970's (Brånemark et al., 1977). Since then the implant has seen many improvements and innovations including transcutaneous systems.

When they were first introduced, percutaneous bone anchored hearing implants were implanted in two stages, where the screw was placed surgically (first stage) and another

intervention was done to attach the abutment (second phase). Currently, almost all implant centers worldwide opt for a single stage procedure where the two phases are done in a single operative procedure. Once the implant is in place, they are left to heal before loading to allow adequate osseointegration with limited micromotion at the bone-implant interface. Several progresses in surgical approaches to implant installation have emerged. These will be discussed in Chapter 4 of this thesis.

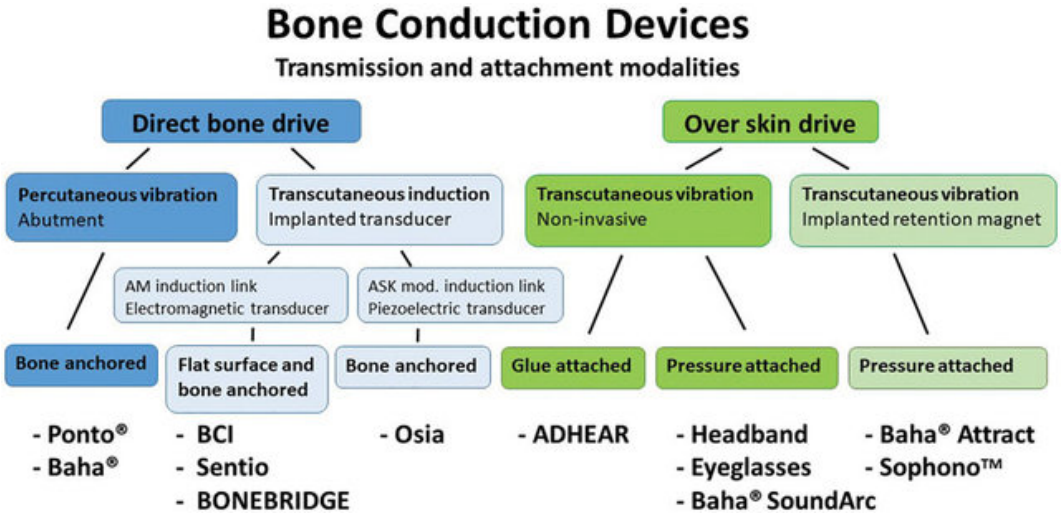

Figure 17. Diagram showing present modalities of bone conduction devices that can be either directly attached to the skull bone (Direct bone drive) or applied over the intact skin (Over skin drive) (Håkansson et al., 2019).

Direct bone conduction hearing systems transfer sound through an osseointegrated implant in the mastoid portion of the temporal bone (Tjellström et al., 1983). A skin-penetrating abutment is added to the implant with the help of a screw and the sound processor is attached. These types of percutaneous devices provide optimal hearing rehabilitation and auditory gain via the bone conduction pathway. The drawbacks of these systems are mostly due to its skin penetration nature causing skin reactions and less favourable aesthetic outcomes (Reinfeldt et al., 2015). Recently,

transcutaneous bone conduction hearing systems have emerged to overcome the drawbacks of the percutaneous system.

Transcutaneous systems can be “over skin drive” or a part of the “direct bone drive”. Direct bone drive systems are also known as active devices because the transducer is implanted under the skin and the vibrations are transmitted directly to the bone. Although the vibrations are directly in the bone, the electromagnetic signal from the sound processor is still transmitted through the skin. Over the skin drive implant are also referred to as passive devices because the transducer is outside the skin and the vibrations from the sound processor are external thus, must be transmitted through the skin. Transcutaneous systems eliminate the need for post-operative skin care and potential skin reactions around the abutment which are commonly seen with percutaneous devices. Transcutaneous systems have their own challenges. The magnetic attachment force must be strong enough to provide a stable fixation for a prolonged time of wear. However, this arises potential for discomfort and skin complications associated with the prolonged skin pressure (necrosis) (Reinfeldt et al., 2015). This can be particularly problematic for the over skin-drive (passive) devices because the magnetic attachment force must be strong enough to provide good transmission of vibrations through the skin. Another limitation of transcutaneous devices is providing adequate power to achieve good audiological results despite attenuations that might occur during skin transfer (Reinfeldt et al., 2015). This will be further discussed in Chapter 5 of the thesis.

References

Aitkin, L. M., Webster, W. R., Veale, J. L., & Crosby, D. C. (1975). Inferior colliculus. I. Comparison of response properties of neurons in central, pericentral, and external nuclei of adult cat. *Journal of Neurophysiology*, *38*(5), 1196–1207. https://doi.org/10.1152/jn.1975.38.5.1196

FirstYears. (n.d.). *Ear*. http://firstyears.org/anatomy/ear.htm

Healthfavo. (2014). *Inner ear bones*. http://healthfavo.com/inner-ear-bones.html

Akagawa, Y., Hashimoto, M., Kondo, N., Satomi, K., Takata, T., & Tsuru, H. (1986). Initial bone-implant interfaces of submergible and supramergible endosseous single-crystal sapphire implants. *The Journal of Prosthetic Dentistry*, *55*(1), 96–100. https://doi.org/10.1016/0022-3913(86)90083-1

Akagawa, Y., Ichikawa, Y., Nikai, H., & Tsuru, H. (1993). Interface histology of unloaded and early loaded partially stabilized zirconia endosseous implant in initial bone healing. *The Journal of Prosthetic Dentistry*, *69*(6), 599–604. https://doi.org/10.1016/0022-3913(93)90289-Z

Almukhtar, Naseer & Obayes, Beshaer & Alturaihy, Safaa. (2013). Electrophysiological Assessment for Children with Sensory Neural Hearing Impairment. *Medical Journal of Babylon.* 10,530-536.

Albrektsson, T., Brånemark, P. I., Hansson, H. A., & Lindström, J. (1981). Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man. *Acta Orthopaedica Scandinavica*, *52*(2), 155–170. https://doi.org/10.3109/17453678108991776

Bayliss, L., Mahoney, D. J., & Monk, P. (2012). Normal bone physiology, remodelling and its hormonal regulation. *Surgery*, *30*(2), 47–53. https://doi.org/10.1016/j.mpsur.2011.12.009

Bear, M. F., Connors, B. W., & Paradiso, M. A. (2007). *Neuroscience Exploring the brain*. Lippincott Williams & Wilkins.

Bellido, T., Plotkin, L. I., & Bruzzaniti, A. (2019). Bone cells. In *Basic and Applied Bone Biology* (pp. 37–55). Academic Press. https://doi.org/10.1016/B978-0-12-813259-3.00003-8

Bess, F. H., & Humes, L. (2008). *Audiology: the fundamentals*. Lippincott Williams & Wilkins.

Bezdjian, A., Smith, R. A., Thomeer, H. G. X. M., Willie, B. M., & Daniel, S. J. (2018). A systematic review on factors associated with percutaneous bone anchored hearing implants loss. *Otology & Neurotology*, *39*(10), e897-e906. https://doi.org/10.1097/MAO.0000000000002041

Botella, J. (n.d.). *What is an audiogram and how to read it*. Hear. https://www.hear.com/resources/all-articles/what-is-audiogram-how-to-read-it/

Brånemark, P. I., Zarb, G. A., & Albrektsson, T. (1985). *Tissue-Integrated Prostheses: Osseointegration in Clinical Dentistry*. Quintessence Publishing Company Inc.

Brånemark, P. I., Hansson, B. O., Adell, R., Breine, U., Lindström, J., Hallén, O., & Ohman, A. (1977). Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period. *Scandinavian Journal of Plastic and Reconstructive Surgery. Supplementum*, *16*, 1–132.

Britannica. (2013). Bone remodeling. In *Encyclopædia Britannica*. https://www.britannica.com/science/bone-remodeling

Brunski, J. B. (1992). Biomechanical factors affecting the bone-dental implant interface. *Clinical Materials*, *10*(3), 153–201. https://doi.org/10.1016/0267-6605(92)90049-Y

Brunski, J. B., Moccia, A. F., Pollack, S. R., Korostoff, E., & Trachtenberg, D. I. (1979). The influence of functional use of endosseous dental implants on the tissue-implant interface. I. Histological aspects. *Journal of Dental Research*, *58*(10), 1953–1969. https://doi.org/10.1177/00220345790580100201

Buckwalter, J. A., Glimcher, M. J., Cooper, R. R., & Recker, R. (1996). Bone biology. II: Formation, form, modeling, remodeling, and regulation of cell function. *Instructional course lectures*, *45*, 387-399.

Burr, D. B. (2019). Bone morphology and organization. In *Basic and Applied Bone Biology* (pp. 3–26). Academic Press. https://doi.org/10.1016/B978-0-12-813259-3.00001-4

Cameron, H. U., Pilliar, R. M., & MacNab, I. (1973). The effect of movement on the bonding of porous metal to bone. *Journal of Biomedical Materials Research*, *7*(4), 301–311. https://doi.org/10.1002/jbm.820070404

Davies, J. E. (2003). Understanding peri-implant endosseous healing. *Journal of Dental Education*, *67*(8), 932–949. https://doi.org/10.1002/j.0022-0337.2003.67.8.tb03681.x

Deporter, D. A., Watson, P. A., Pilliar, R. M., Chipman, M. L., & Valiquette, N. (1990). A histological comparison in the dog of porous-coated vs. Threaded dental implants. *Journal of Dental Research*, *69*(5), 1138–1145. https://doi.org/10.1177/00220345900690050401

Ducheyne, P., Meester, P. de, & Aernoudt, E. (1977). Influence of a functional dynamic loading on bone ingrowth into surface pores of orthopedic implants. *Journal of Biomedical Materials Research*, *11*(6), 811–838. https://doi.org/10.1002/jbm.820110603

Ellingsen, J. E., & Lyngstadaas, S. P. (2003). *Bio-implant interface: Improving biomaterials and tissue reactions / [edited by] Jan Eirik Ellingsen, S. Petter Lyngstadaas*. CRC Press.

Gelfand, S. A. (2009). *Essentials of audiology.* Thieme.

Håkansson, B., Reinfeldt, S., Persson, A.-C., Jansson, K.-J. F., Rigato, C., Hultcrantz, M., & Eeg-Olofsson, M. (2019). The bone conduction implant - a review and 1-year follow-up. *International Journal of Audiology*, *58*(12), 945–955. https://doi.org/10.1080/14992027.2019.1657243

Hashimoto, M., Akagawa, Y., Nikai, H., & Tsuru, H. (1988). Single-crystal sapphire endosseous dental implant loaded with functional stress--clinical and histological evaluation of peri-implant tissues. *Journal of Oral Rehabilitation*, *15*(1), 65–76. https://doi.org/10.1111/j.1365-2842.1988.tb00147.x

Hudspeth, A. J. (1989). How the ear's works work. *Nature*, *341*(6241), 397–404. https://doi.org/10.1038/341397a0

Hudspeth, A. J. (1992). Hair-bundle mechanics and a model for mechanoelectrical transduction by hair cells. *Society of General Physiologists Series*, *47*, 357–370.

Jahn, A. F., & Santo-Sacchi, J. (2001). *Physiology of the ear*. Cengage Learning.

Katz, J., & Lezynski, J. (2002). Clinical masking. In J. Katz (ed.), *Handbook of clinical audiology* (5th ed., pp. 124–141), Lippincott Williams & Wilkins.

Kelion, L. (2013, July 3). *Talking train window adverts tested by Sky Deutschland.* BBC. https://www.bbc.com/news/technology-23167112?SThisFB

Lum, L. B., Beirne, O. R., & Curtis, D. A. (1991). Histologic evaluation of hydroxylapatite coated versus uncoated titanium blade implants in delayed and immediately loaded applications. *International Journal of Oral & Maxillofacial Implants*, *6*(4), 150–161.

Mann, Z. F., & Kelley, M. W. (2011). Development of tonotopy in the auditory periphery. *Hearing Research*, *276*(1-2), 2–15. https://doi.org/10.1016/j.heares.2011.01.011

Marieb, E. N., Mallatt, J., & Wilhelm, P. B. (2008). *Human anatomy* (5th ed.) Benjamin Cummings.

Mavrogenis, A. F., Dimitriou, R., Parvizi, J., & Babis, G. C. (2009). Biology of implant osseointegration. *Journal of Musculoskeletal & Neuronal Interactions*, *9*(2), 61–71.

Musiek, F. E., Weihing, J. A., Oxholm, V. B. (2007). *Anatomy and physiology of the Central Auditory Nervous System: A Clinical Perspective*. Thieme.

Oticon Medical. (n.d.). *How bone conduction systems work | Oticon Medical*. Retrieved November 25, 2020, from https://www.oticonmedical.com/bone-conduction/new-to-bone-conduction/what-is-bone-conduction/how-bone-conduction-systems-work

Paul, P. V., & Whitelaw, G. M. (2010). *Hearing and deafness, 308*. Jones & Bartlett Publishers.

Raphael, Y., & Altschuler, R. A. (2003). Structure and innervation of the cochlea. *Brain Research Bulletin*, *60*(5-6), 397–422. https://doi.org/10.1016/S0361-9230(03)00047-9

Reinfeldt, S., Håkansson, B., Taghavi, H., & Eeg-Olofsson, M. (2015). New developments in bone-conduction hearing implants: A review. *Medical Devices (Auckland, N.Z.)*, *8*, 79–93. https://doi.org/10.2147/MDER.S39691

Salvi, R., Sun, W., & Lobarinas, E. (2007). *Anatomy and physiology of the peripheral auditory system*. Thieme.

Samra, B. (2018, April 16). *Bone Anchored Hearing Systems - Principles and Candidacy Barinder Samra.* Audiology Online. https://www.audiologyonline.com/articles/bone-anchored-hearing-systems-principles-22366

Schatzker, J., Horne, J. G., & Sumner-Smith, G. (1975). The effect of movement on the holding power of screws in bone. *Clinical Orthopaedics and Related Research*(111), 257–262. https://doi.org/10.1097/00003086-197509000-00032

Szmukler-Moncler, S., Salama, H., Reingewirtz, Y., & Dubruille, J. H. (1998). Timing of loading and effect of micromotion on bone-dental implant interface: Review of experimental literature. *Journal of Biomedical Materials Research*, *43*(2), 192–203. https://doi.org/10.1002/(SICI)1097-4636(199822)43:2<192::AID-JBM14>3.0

Tjellström, A., Rosenhall, U., Lindström, J., Hallén, O., Albrektsson, T., & Brånemark, P. I. (1983). Five-year experience with skin-penetrating bone-anchored implants in the temporal bone. *Acta Oto-Laryngologica*, *95*(5-6), 568–575. https://doi.org/10.3109/00016488309139444

Uhthoff, H. K. (1973). Mechanical factors influencing the holding power of screws in compact bone. *The Journal of Bone and Joint Surgery. British Volume*, *55-B*(3), 633–639. https://doi.org/10.1302/0301-620X.55B3.633

Wang, Y., Zhang, Y., & Miron, R. J. (2016). Health, maintenance, and recovery of soft tissues around implants. *Clinical Implant Dentistry and Related Research*, *18*(3), 618–634. https://doi.org/10.1111/cid.12343

Westover, L., Faulkner, G., Hodgetts, W., & Raboud, D. (2016). Advanced system for implant stability testing (ASIST). *Journal of Biomechanics*, *49*(15), 3651–3659. https://doi.org/10.1016/j.jbiomech.2016.09.043

World Health Organization. (2020, March 1). Deafness and hearing loss. https://www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss

Chapter 2

Thesis Rationale and Aims

2.1 Rationale

Prosthetic implants are most commonly used in the dental and orthopaedic fields (Tjellström et al., 1983). Bone anchored implants relies on the structural integration between the implant surface and its surrounding bone, termed osseointegration (Brånemark et al., 1985). The conditions to promote osseointegration of an implant include biocompatibility of the implant surface material (e.g. titanium), minimal trauma to the bone during the surgical installation, and an immobile healing phase (Brånemark et al., 1985). During this healing phase bone is deposited onto the implant surface and remodeling occurs resulting in a bone-implant interface in which the implant is directly connected to the living bone. The success of these implants is dependent on the process of osseointegration at the bone-implant interface. The primary objectives of prosthetic implants are to enhance functionality and/or improve aesthetics. Prosthetic implants are most commonly used in the dental and orthopaedic fields. However, they are also used in prosthetic reconstruction in the head and neck area. For example, implants can be designed and surgically placed to reconstruct dental arches, to install bone anchored hearing implants and/or prosthetic ears, or to build craniofacial structures after trauma. The use of implants in such applications significantly improves functionality and overall quality of life.

The bone anchored hearing implant involves surgically installing a titanium screw into the temporoparietal skull bone. Attached to this screw is an abutment that permanently penetrates the skin surface and the device so that a sound processor can then be attached. While the long-term success rate is very high, implant losses do occur at a rate of less than 10% (Dun et al., 2012; Fontaine et al., 2014; Bezdjian et al., 2018). Sometimes occurring spontaneously and without any known cause, implant losses can happen even years after placement. The literature around why

these implants extrude, rates of extrusion, and ways to prevent extrusion is lacking (Bezdjian et al., 2018).

Moreover, there is uncertainty in the optimal time to begin functional loading of the bone anchored auditory systems. Clinicians and researchers have not been able to answer the following question: *How much time does the bone-implant surface need to sufficiently osseointegrate so that the bear loading sound processor can be coupled?* From the patient perspective, especially in children, it would be beneficial to load the sound processor as soon as possible after surgery to shorten the detrimental period of auditory deprivation and allow auditory and social development by experiencing significant functional improvements. To load the sound processor to the percutaneous implant screw via the abutment, proper healing of the skin surrounding the area needs to be achieved and adequate osseointegration is necessary for the success of the implant. Unlike skin healing, the integrity of the bone-implant healing cannot be determined in the clinical setting. Thus, currently there is a large variation observed in reported clinical protocols advocating timing before sound processor coupling.

Most of the bone-implant interface research in the existing literature is conducted in the dental and orthopeadic fields. Although similarities are imminent, there are some differences that need to be explored. Bone healing around implants involves a cascade of cellular events which necessitates a rich blood supply near the implant surface. Compared to dental implants, the auditory implants are in a completely different microbial spectrum and bone composition, and compared to orthopeadic implants, auditory implants have different load bearing properties.

The classic bone anchored hearing implant is percutaneous in nature. Thus, a skin-penetrating abutment is present to attach the sound processor. The drawbacks of these systems are mostly due to its skin penetration nature causing skin reactions and less favourable aesthetic

outcomes (Reinfeldt et al., 2015). Skin reactions are common. However, there is no consensus on the classification and treatment of skin reactions around the implant site. More recently, transcutaneous bone conduction hearing systems have emerged to overcome the drawbacks of the percutaneous system. Although appealing aesthetically, it has been suggested that auditory gain isn't comparable to the percutaneous system due to skin attenuation.

2.2 Aims

This main objective of this thesis was to investigate factors influencing the biological and clinical outcomes following the installation of bone anchored hearing implants. The key factors that were evaluated were devices types, bone-implant characteristics, surgical approaches, auditory gains, skin healing, and factors associated with implant loss.

The specific aims of the papers included in this thesis were as followed:

- To identify factors associated with percutaneous bone anchored hearing implant loss in a systematic review [Paper I].
- To determine if peri-operative resonance frequency analysis can determine the optimal processor coupling time [Paper II]
- To evaluate age-related changes in the skull bone that influences the stability of bone anchored hearing implants in a cadaveric study [Paper III].
- To underline the affect smoking has on bone anchored hearing implant loss in a case report and review of literature [Paper IV].
- To delineate if skin thinning has advantages in post-operative skin healing compared to tissue preservation during surgery via a systematic review [Papers V & VI].
- To compare outcomes from two surgical approaches to percutaneous bone anchored hearing implants in a retrospective cohort [Paper VII].

- To compare three commonly used skin tolerability classification scales for post-operative skin healing assessment [Paper VIII].
- To present a technical note describing a challenging case of replacing an abutment [Paper IX].
- To explore a transcutaneous system and describe its advantages and disadvantages [Papers X & XI].

Chapter 3

Implant loss, stability and osseointegration

A Systematic Review on Factors Associated with Percutaneous Bone Anchored Hearing Implants Loss

Aren Bezdjian, Rachel Ann Smith, Henricus G.X.M. Thomeer, Bettina M. Willie, Sam J. Daniel

Published in: Otology & Neurotology 2018 Dec;39(10):e897-e906.

ABSTRACT

Objective: To investigate factors associated with percutaneous bone anchored hearing implant (BAHI) loss.

Data Sources: Africa-Wide, Biosis, Cochrane, Embase, Global Health, LILACs, Medline, Pubmed, and Web of Science electronic databases.

Study Selection: All studies reporting on adult and/or pediatric patients with a BAHI loss were identified. Retrieved articles were screened using predefined inclusion criteria. Eligible studies underwent critical appraisal for directness of evidence and risk of bias. Studies that successfully passed critical appraisal were included for data extraction.

Data Extraction: Extracted data included study characteristics (study design, number of total implants and implant losses, follow up), patient characteristics (gender, age, comorbidities, previous therapies) and information regarding BAHI loss (etiology of loss, timing of occurrence).

Data Synthesis: From the 5151 articles identified at the initial search, 847 remained after title and abstract screening. After full text review, 96 articles were eligible. 51 articles passed quality assessment, however, due to overlapping study population, 48 articles reporting on 34 separate populations were chosen for data extraction. 301 implant losses occurred out of 4116 implants placed, resulting in an overall implant loss occurrence rate of 7.3%. Failed osseointegration was responsible for most implant losses (74.2%), followed by fixture trauma (25.7%). Most losses due to failed osseointegration occurred within 6 months of the implantation. BAHI implant loss occurred more frequently in pediatric patients ($p < 0.005$).

Conclusion: The current systematic review identified factors associated with BAHI loss. These factors should be considered when assessing patients' candidacy and when investigating reasons for impeded implant stability and loss.

INTRODUCTION

The bone anchored hearing implant (BAHI) was developed in the 1970s as a solution for conductive and mixed hearing loss.[1] For the past three decades, bone anchored hearing implants have been used effectively as a treatment for conductive or mixed hearing loss.[1,2,3] BAHIs utilize the body's natural ability to transfer sound through the skull bone and successfully rehabilitate hearing-impaired individuals. These systems are based on the principle of osseointegration; a dynamic process of bone regeneration and remodeling.

The most frequently implanted BAHIs use an osseointegrated percutaneous titanium screw to transmit sound vibrations, generated by an external auditory processor, to the temporal bone to be sensed by the cochlea. Complications related to the percutaneous nature of the implant exists. Although most adverse events associated with the percutaneous BAHI are skin-related, implant losses occur, sometimes spontaneously without any known cause.[4,5] Various factors that compromise implant-bone stability causing implant losses heave been identified. These include recipient age, recipient bone mass and quality, certain medications, comorbidities such as diabetes mellitus, and previous exposure to radiotherapy.[6-8] BAHI failure rates have been reported to vary from 0% to 26%.[2,7,8]

Over the last decade, the percutaneous BAHI has seen many design and surgical innovations. Improved surgical approaches successfully decreased operative time and peri-operative complications, while wider screws with roughened surfaces demonstrated improved implant stability. These changes have resulted in lower implant loss rates.[9-11] Risk factors associated with BAHI losses remain to be elucidated.

The current literature on hearing rehabilitation with percutaneous BAHIs consists of several cohort series that report BAHI losses. The aim of this study was to systematically review

studies reporting BAHI losses in order to investigate factors associated with implant loss, determine causes of loss and predict which recipient could be susceptible to a future implant loss.

METHODS

The systematic review was conducted in concordance with PRISMA guidelines.[12]

Search Strategy

The McConnell Resource Centre of the McGill University Health Centre performed a comprehensive search in nine electronic databases Africa-Wide, Biosis, Cochrane, Embase, Global Health, LILACs, Medline, Pubmed and Web of Science to identify BAHI recipients in the current literature. Search terms used were ‘‘bone anchored hearing device/aids,’’ ‘‘bone conduction,’’ ‘‘osseointegration”, and synonyms. A complete search strategy per database can be acquired on Appendix 1 (Supplemental Digital Content 1). Search results were gathered from inception until the search date of February 10, 2017.

Terms Used	Variations of Terms to use when searching
Bone anchored hearing aids/devices	• (bone* adj5 anchor*).tw,kf. • (BAHA or BAHAs or "BAHA’s" or BAHI or BAHIs or "BAHI’s").tw,kf. • (divino or intenso or cordelle).tw,kf. • (HC adj1 ("100" or "200" or "210" or "220" or "300" or "360" or "380" or "400")).tw,kf.
Bone conduction	• Bone Conduction/ • ((bone* adj5 conduct*) or osteoconduct* or osteo-conduct*).tw,kf.
Osseointegration	• Osseointegration/ • (((bone* or osseo*) adj5 integrat*)) or osseointegrat).tw,kf.
Hearing aids/implants	• exp Hearing Aids/ • ((hear* or ear* or deaf* or auditor* or audiolog* or auricul* or cochlea* or ossic* or tympan* or vestib* or otol* or otorhin* or otorrin* or neurootol*) adj4 (aid* or device* or implant* or prosthes*)).tw,kf. • (Hearing/ or Hearing Loss/ or exp Ear/) AND (exp Prosthesis Implantation/ or exp "Prostheses and Implants"/)

Suppl. Digital Content 1. Search strategy per database gathered from inception until the search date of February 10, 2017.

Study Selection

Articles presenting both adult and pediatric patients with a percutaneous BAHI loss were identified. Articles written in English or French were included. Exclusion criteria included non-human studies and transcutaneous systems. Articles presenting patients with voluntary BAHI surgical removals were also excluded. When the same population or data were presented in more than one publication, the data were combined or the most recent study was selected.

Quality Assessment

All eligible articles were critically appraised for directness of evidence (DoE) and risk of bias (RoB) by two authors (AB and RAS) using predefined criteria. DoE was assessed using six criteria; demographic data, indication for implantation, description of surgical procedure, etiology and timing of implant failure and follow-up. RoB was assessed using standardization of surgical procedure, standardization of outcomes, standardization of follow-up, and missing data.

The DoE assessment was scored as high when scores were at least 4 out of a possible 6, as moderate when scores were 3 or 3.5, and as low with scores below 3. The RoB assessment based on the Cochrane Collaboration's tool for assessing RoB was scored as low when scores were at least 3 out of a possible 4, as moderate when scores were 2 or 2.5, and as high with scores lower than 2. Articles included for data extraction scored: (1) high for DoE and low for RoB or (2) high for DoE and moderate for RoB (Table 1a,b).

Table 1a. Critical appraisal of selected studies

			Directness of evidence (DoE)							Risk of bias (RoB)				
Authors	**Publication year**	**Study design**	**Demographic data**	**Indication for implantation**	**Description of surgery**	**Etiology of implant failure**	**Timing of implant failure**	**Follow-up**	**DoE Score**	**Standardization (S)**	**Standardization (O)**	**Standardization (FU)**	**Missing data**	**RoB Score**
Ali *et al.*	2009	RCS	●	●	●	●	●	●	**H**	○	◑	●	●	M
Asma *et al.*	2013	RCS	◑	●	●	●	●	◑	**H**	◑	●	◑	●	M
Bejar-Solar *et al.*	2000	PCS	●	●	●	●	●	●	**H**	◑	●	◑	●	M
Bouhabel *et al.*	2012	RCS	●	●	●	●	●	●	**H**	●	●	●	●	L
Calvo Bodnia *et al.*	2014	RCS	●	●	◑	●	●	◑	**H**	◑	●	●	●	L
Christensen *et al.*	2010	RCS	●	●	●	●	○	●	**H**	●	●	●	●	L
Darley *et al.*	2013	RCS	◑	●	○	●	●	◑	**H**	◑	◑	◑	◑	M
de Wolf *et al.*	2008	RCS	◑	●	●	●	●	◑	**H**	◑	●	◑	◑	M
de Wolf *et al.*	2009	RCS	●	●	●	●	●	◑	**H**	◑	●	◑	◑	M
den Besten *et al.*	2016	RCT	◑	○	●	●	●	●	**H**	◑	●	●	◑	M
Doshi *et al.*	2010	RCS	◑	●	○	●	●	◑	**H**	◑	●	◑	●	M
Dumon *et al.*	2016	PCS	◑	●	●	●	○	◑	**H**	◑	●	◑	●	M
Dun *et al.*	2010	RCS		●										
Dun *et al.*	2011	RCI	◑	◑	●	●	●	◑	**H**	◑	●	●	●	L
Dun *et al.*	2012	RCS	◑	●	●	◑	●	◑	**H**	◑	◑	◑	◑	M
Faber *et al.*	2009	RCS	●	●	●	●	○	●	**H**	◑	●	◑	●	M
Faber *et al.*	2012	PCS	●	○	●	●	●	◑	**H**	●	●	●	●	L

House *et al.*	2007	RCS	●	●	●	◑	●	○	**H**	◑	●	○	●	M
Hultcrantz *et al.*	2014	RCS	●	●	●	◑	○	●	**H**	◑	◑	◑	●	M
Johansson *et al.*	2017	PMCI	●	○	●	●	●	◑	**H**	◑	●	○	◑	M
Kraai *et al.*	2011	RCS	●	●	●	●	○	◑	**H**	●	●	◑	●	L
Lanis *et al.*	2013	RCS	●	●	◑	●	○	◑	**H**	◑	●	◑	●	M
Larsson *et al.*	2015	RCS	◑	◑	◑	●	●	◑	**H**	◑	●	◑	◑	M
Lustig *et al.*	2001	RCS	●	●	●	●	○	○	**H**	○	●	○	●	M
McDermott *et al.*	2009	RCS	●	●	●	◑	◑	●	**H**	◑	◑	◑	◑	M
McLarnon *et al.*	2014	PCS	●	●	◑	●	○	◑	**H**	●	●	●	●	L
Mylanus *et al.*	1994	RCS	◑	●	●	●	○	◑	**H**	●	●	◑	●	L
Nelissen *et al.*	2016	RCS	◑	●	○	◑	●	●	**H**	◑	●	◑	●	M
Nelissen *et al.*	2013	RCS	●	●	●	●	●	●	**H**	●	●	◑	●	L
Nelissen *et al.*	2014	RCI	●	●	○	●	●	●	**H**	○	●	◑	●	M
Rebol.	2015	RCS	◑	●	◑	●	●	●	**H**	○	●	◑	●	M
Saliba *et al.*	2010	PCS	●	●	●	●	●	●	**H**	●	●	◑	●	L
Saliba *et al.*	2012	RCS	◑	○	●	●	●	◑	**H**	◑	●	◑	●	M
Seemann *et al.*	2004	RCS	◑	●	●	●	◑	◑	**H**	◑	●	◑	●	M
Strijbos *et al.*	2017	RCS	◑	●	●	●	●	●	**H**	◑	●	●	●	L
Tietze *et al.*	2001	RCS	●	●	●	●	●	◑	**H**	◑	●	●	●	L
Tjellstrom *et al.*	1994	RCS	◑	●	●	◑	◑	●	**H**	●	◑	◑	◑	M
Van der Gucht *et al.*	2017	RCS	◑	●	●	●	◑	◑	**H**	◑	●	◑	●	M
Van der Pouw *et al.*	1999B	RCS	◑	●	○	●	●	●	**H**	○	●	◑	◑	M

Wade *et al.*	2002	RCS	◑	●	●	◑	○	●	**H**	◑	◑	◑	●	M
Wallberg *et al.*	2011	RCS	◑	●	●	●	◑	◑	**H**	◑	●	◑	◑	M
Amonoo-Kuofi *et al.*	2015	RCS	●	●	●	○	○	◑	**M**	◑	◑	◑	●	M
Badran *et al.*	2009	RCS	◑	●	◑	●	○	◑	**M**	◑	◑	◑	●	M
Dun *et al.*	2010	RCS	●	●	○	○	●	○	**M**	○	●	○	●	M
Exley *et al.*	2012	CR	●	◑	○	●	●	○	**M**	●	●	○	●	M
Fuchsmann *et al.*	2010	RCS	◑	●	○	◑	●	◑	**M**	◑	●	◑	●	M
Kompis *et al.*	2017	RCS	●	●	○	●	○	○	**M**	○	●	○	●	M
Macnamara *et al.*	1996	RCS	○	●	○	◑	○	◑	**L**	○	○	◑	●	H
Muzaffar *et al.*	2014	RCS	●	○	●	○	●	○	**M**	●	◑	○	●	M
Ricci *et al.*	2010	RCS	◑	●	○	◑	○	◑	**L**	○	●	◑	●	M
Shirazi *et al.*	2006	RCS	◑	●	●	●	○	○	**M**	○	●	○	●	M
Tjellstrom *et al.*	1995	RCS	◑	●	●	●	○	○	**M**	◑	●	○	◑	M
Tjellstrom *et al.*	2012	RCS	◑	○	○	●	●	●	**M**	○	○	◑	◑	H
Van der Pouw *et al.*	1999 A	RCS	○	●	●	●	○	◑	**M**	◑	●	◑	◑	M
Wazen *et al.*	2008	RCS	◑	●	○	◑	●	◑	**M**	○	●	◑	●	M
Yellon	2007	RCS	●	○	○	●	○	◑	**L**	◑	○	◑	●	M
Zeitoun *et al.*	2002	RCS	●	◑	●	◑	○	◑	**M**	○	◑	◑	◑	H

Table 1b. Assessment per item for critical appraisal of selected studies

	Grading (● = 1 point, ◑ = 0.5 point, ○ = 0 point)
Study design	RCS, retrospective case series PCS, prospective case series PMCI, prospective multicenter clinical investigation RCT, randomized controlled trial RCI, randomized clinical investigation SS, survey study CR, case report
Directness of Evidence (DoE)	
Demographic data of patient(s) with failed implant *Age at treatment* *Laterality* *Gender* *Comorbidities*	individually reported or pediatric/adult cohort, ● mean or range reported, ◑ not reported, ○
Indication for implantation *Etiology of hearing loss*	reported, ● reported but not per patient or reported as unknown, ◑ not reported, ○
Description of surgery *Single or two-stage procedure* *Surgical details*	described, ● not clearly described, ◑ not described, ○
Etiology of implant loss *Primary or secondary failure* *Description of failure*	described, ● unknown or not described, ◑ not reported, ○
Timing of implant loss *When failure occurred*	reported, ● mean reported, ◑ not reported, ○
Follow-up *Duration of follow-up of patients included in the study*	> 1 year, ● < 1 year, ◑ not reported, ○
Overall DoE score	High, ≥ 4 points Moderate, between 3-4 points Low, < 3
Risk of Bias (RoB)	
Standardization of surgery *Same surgical approach, implant and loading time*	all patients underwent the same surgery and implant, ● different types of surgery or implant, ◑ surgical outcomes not described, ○
Standardization of outcome *Outcomes related to implant*	identical outcome reports, ● reported however not standardized, ◑ not reported, ○
Standardization of follow up	identical follow up for all patients, ● reported however not standardized, ◑ not reported, ○
Missing data	no missing data; missing data mentioned/quantified and method of handling described, ● missing data mentioned but method of handling not described, ◑ missing data not reported, ○
Overall RoB score	Low, ≥ 3 points Moderate, between 2-3 points High, < 2

Data Extraction

Data was extracted from articles which successfully passed critical appraisal. Extracted data included study characteristics such as study design, number of BAHIs implanted and lost, and follow up time. Patient characteristics such as gender, age, comorbidities and previous therapies were extracted when available. Information pertaining to the nature and timing of the BAHI loss in each study were also reviewed.

RESULTS

Database Search and Critical Appraisal

The study selection process is summarized in a flow chart (Figure 1). The initial database search retrieved 5151 entries. After screening title and abstract, 847 were selected for full text review. 96 articles met the inclusion criteria and were critically appraised. Of these articles, 51 passed quality assessment. Three articles were excluded due to overlapping cohorts providing no new data. The majority of articles were retrospective case series reports. Six articles described prospective studies (Table 1a). Of the 48 remaining articles, 14 were found to have overlapping data. Some of the overlapping data was combined, leading to 34 unique study populations.

In total, there were 4116 BAHI surgeries performed, of which 301 implants were lost. This represents an overall failure rate of 7.3% in this series (Table 2). 14 studies included pediatric patients and 6 studies reported on solely adult populations. 14 studied combined adult and pediatric populations. The majority of the included studies (n = 17) had a mean follow up time of over 2 years.

Figure 1. Flow chart demonstrating study selection process

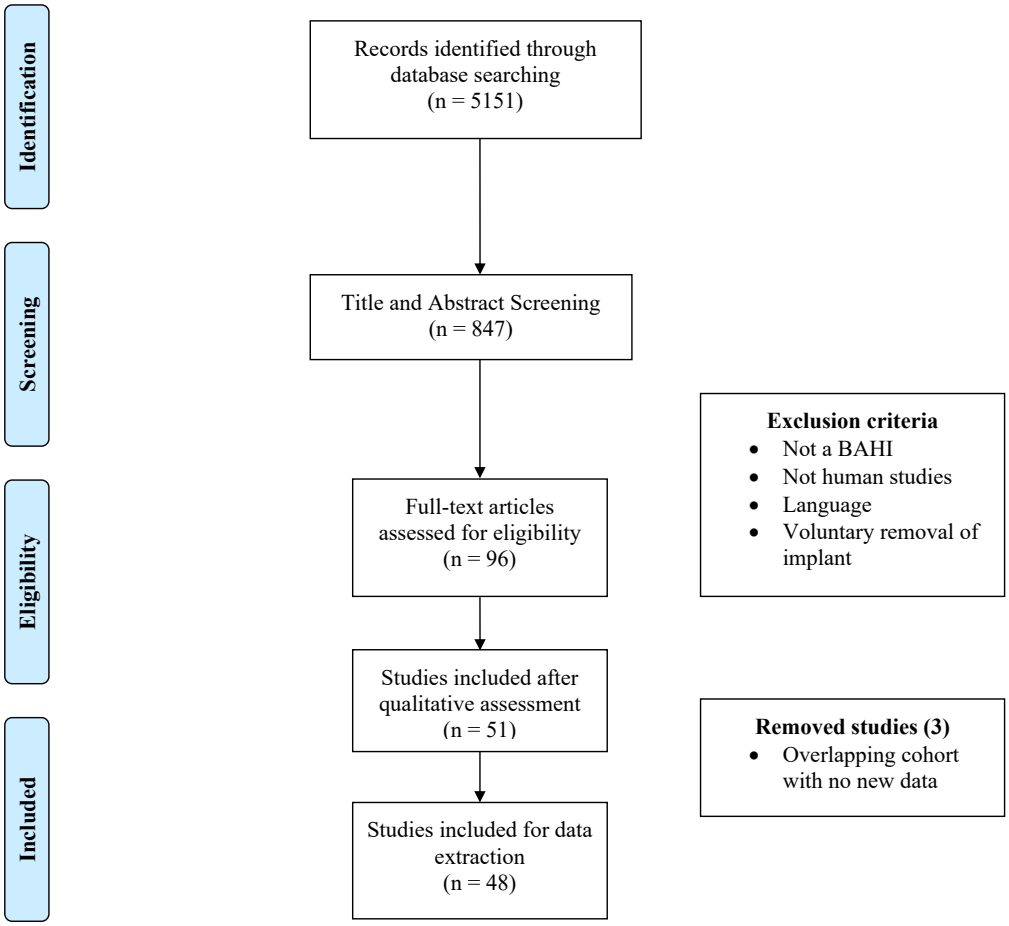

Table 2. Study characteristics of included articles

Study characteristic	Total
n, included studies for data extraction	48
n, different study populations	34
n, implants	4116
n, implants losses	292
Failure rate	7.1 %
n, studies reporting on:	
Pediatric	14
Adults	6
Both	14
n, studies reporting follow up	
<6 months	1
6 months – 1 year	2
1 – 2 years	8
>2 years	17
NS	6

Patient Characteristics

There was a total of 718 pediatric and 839 adult BAHI recipients identified. When available, potential causes behind BAHI loss was poor bone quality or bone abnormality such as uneven skull surface. This finding was specified in 8 patients (Table 3). Of these observations, a surgeon noticed, intra-operatively, an adult patient with soft skull bone causing the implant to move with manual manipulation, while another encountered challenges during drilling and screw placement due irregular bone surface. Other observations included insufficient bone thickness discovered intra-operatively while drilling in two children. Six patients with a BAHI loss had previously received radiotherapy to the temporoparietal bone area. Other identified factors

associated with BAHI loss were steroid therapy (2), diabetes medication (1), smoking (1), alcohol abuse (1) and being overweight (1).

Of the comorbidities present in patients with BAHI loss, mental retardation (5) and Treacher Collins syndrome (5) were the most common followed by other conditions such as Pierre Robin syndrome (1), Cornelia de Lang syndrome (1), Morbus Addison disease (1), and type 2 diabetes (1) (Table 3). Although the age of patients with comorbidities presenting with a BAHI loss is not always specified, all patients diagnosed with Treacher Collins syndrome in this review were pediatric.

The overall BAHI loss incidence was significantly higher in pediatric populations (63/718; 8.8%) compared to adults (24/839; 2.9%) ($p<0.005$). Of the studies reporting the age of patient presenting with a BAHI loss, a mean age of 22.5 years, ranging from 2.5 to 73 years old, and a median of 10 years was calculated. This data was derived from 29 patients presenting with a BAHI loss, where authors specified the patients' age. 75.9% of these studies presented patients with implant losses who were below the age of 16.

Table 3. Characteristics of patients with BAHI loss reported in the included articles

Patient characteristic	Number of patients
Previous therapies / patient factors	
Poor bone quality or abnormality	8
Radiotherapy	6
Steroid therapy	2
Diabetes medications	1
Heavy smoker	1
Alcohol abuse	1
Overweight	1
Comorbidities	
Mental retardation	5
Treacher Collins syndrome	5
Pierre Robin syndrome	1
Cornelia de Lang syndrome	1
Morbus Addison disease	1
Type 2 diabetes	1
Age in years	
Mean	22.5
Median	10
Range	[2.5 – 73]
Age distribution	
< 4 years	1
4-8 years	4
8-12 years	6
12-16 years	11
16-20 years	2
60-65	3
>65	2
NS	269

BAHI Loss

BAHI losses occurred either due to trauma or a failure to osseointegrate. 75 implants extruded due to trauma (25.7%) and 217 implant losses occurred due to a failure of osseointegration (74.2%) (Table 4). Traumatic losses occurred in 30 out of 718 total implants placed in pediatric patients (4.2%), while only 2 out of 839 implanted BAHIs in adult cohorts (0.2%) were extruded due to trauma. The two most common forms of trauma resulting in implant losses were falls during play (i.e. in playground or school) and physical hits (i.e. by a ball) (Figure 2). Traumatic fixture losses occurred at various different time points after implantation. When available, reported data pertaining to the timing of BAHI losses due to failed osseointegration could occur at any moment following implantation. Extracted data suggests that early failures occurred due to a lack of initial osseointegration occurring within 6 months of implantation, but also spontaneous losses occurred even years after implantation (Table 4).

Figure 2. Identified causes of traumatic BAHI losses

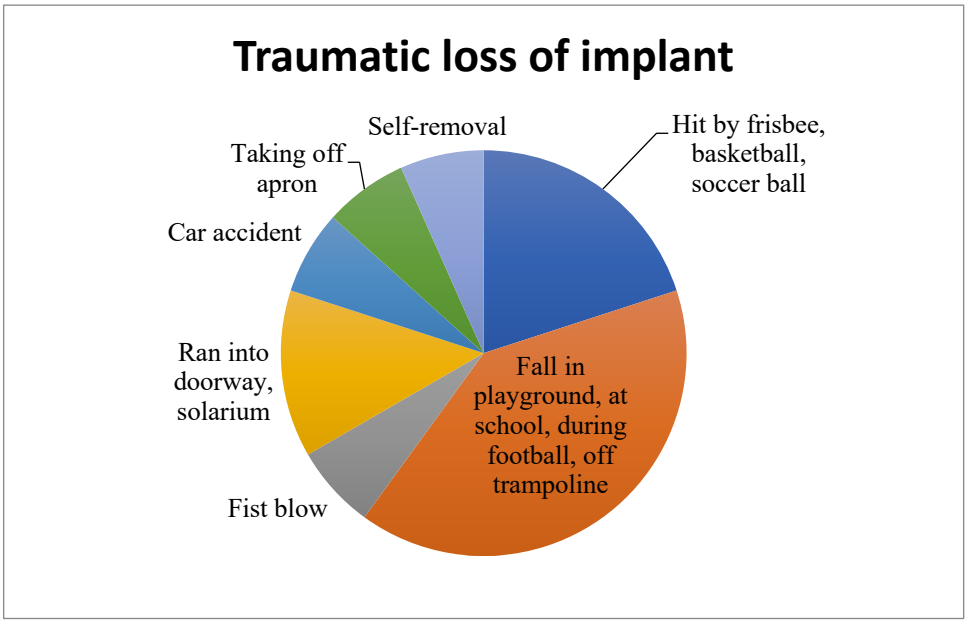

Table 4. BAHI loss characteristics from included articles

Implant Loss		n (%)
Etiology of loss		
Trauma		75 (25.7%)
Failure to osseointegrate		217 (74.2%)
Unknown		9
Patient Age Cohort		
	Pediatric	63/718 (8.%)*
	Adults	24/839 (2.9%)*
	Elderly	4/103 (3.9%)
Traumatic loss		
Pediatric loss due to Trauma		30/718 (4.2%)*
Adult loss due to trauma		2/839 (0.24%)*
Age/age cohort not specified		43
Failure to osseointegrate		
Pediatric loss due to Trauma		33/718 (4.6%)
Adult loss due to trauma		22/839 (2.6%)
Age/age cohort not specified		162
Timing of loss		
	Failure to osseointegrate	
	<6 months	32
	6 months – 1 year	4
	1 – 2 years	8
	>2 years	17
	NS	155
	Traumatic loss	
	<6 months	6
	6 months – 1 year	3
	1 – 2 years	4
	>2 years	16
	NS	46
		*statistically different P<0.005

DISCUSSION

The reported rate of BAHI failure in the literature varies from 0 to 26%. The vast majority of these are based on a small BAHI cohort series. The search strategy applied for the present systematic review included articles with at least one BAHI loss. Therefore, the incidence rate of 7.3% found in 4116 BAHI recipients is an overestimation because studies presenting BAHI patient cohorts with no implant losses were excluded. Also, our study did not include voluntary explantation of implants either by patient request or surgeons' decision due to skin reactions or infection for example. Nonetheless, our incidence rate is still lower than some reports suggesting BAHI losses are likely overestimated in some series and vary according to centers of implant.[8,13] Although implant loss is fairly uncommon, it is important to identify factors that can affect BAHI survival and identify patients that are susceptible for future implant losses.

It is well-known that children are at a higher risk of fixture loss compared to adults. Studies have identified implant failure rates in children to vary from 5.0% to 29.0%, compared to 2.5% to 3.5% in large cohorts of adults.[2,13-17] Comparably, the present review revealed a significantly higher BAHI loss rate in pediatric patients (8.8%; 63/718) when compared to adults (2.9%; 24/839).

Various causes impeding bone-implant stability have been identified in the literature, particularly for dental or orthopedic implants. The systematic review attempted to highlight factors associated with BAHI loss. Unfortunately, only few included studies presenting a patient with a BAHI (20 patients) specified a potential cause behind implant loss. It is therefore, difficult to draw conclusions.

Age-dependent structural bone differences may be related with BAHI losses. Young children can frequently present with softer, thinner, and immature temporal bone compared to

adults. Pediatric skull bone contains air cells generally filled with bone marrow cells and an extensive blood supply.[18] Postoperatively, softer, more compliant bone may not tolerate the BAHI processor load, leading to excessive micromotion during the initial healing phase.[19,20] Thus, this could necessitate a longer osseointegration period and require delayed processor coupling protocols. Also, adequate temporoparietal bone thickness is critical for successful implant osseointegration. High resolution computed tomography (CT) of the temporal bone could be considered before planning BAHI surgery for young children who are suspected of having inadequate bone thickness or quality.

Elderly patients also benefit from BAHIs. However, as the aging process occurs, bone resorption exceeds bone formation, reducing bone mass, increasing bone fragility. Osteoporosis has been shown to be a risk factor for impaired healing and osseointegration.[21-24] There is also an accompanying age-related reduction in the bone formation response to mechanical loading that likely deleteriously affects healing around the implants.[25-27] Due to these factors, it would be beneficial to assess bone mass and quality in elderly patients prior to BAHI implantation.

Rehabilitation of conductive hearing loss with BAHIs has been successfully performed in patients with comorbidities such as trisomy 21, Treacher Collins syndrome or other disabilities commonly presenting with conductive hearing loss.[28-30] In syndromic patients, bone thickness can be insufficient and irregular, presenting with peri-operative challenges and impeding overall implant stability. Marsella et al. recommend assessing candidacy of these patients with a CT scan to evaluate skull thickness and, when appropriate, consider cranial bone augmentation to increase fixture stability.[29] Moreover, inadequate post-operative hygienic care increases the risk of implant site infections and, as a result, is attributed to a higher implant loss incidence in pediatric patients in general.[2,7,30]

Due to their active lifestyles and play activities, children are inherently at higher risk for traumatic implant losses. Almost all BAHI losses identified in this review that were associated with trauma occurred in children. Primarily, these resulted from falls or blows to the implant site during play. During the initial period of osseointegration, the implant must remain immobile. Even if the fixture does not extrude, a traumatic blow to the fixture can jeopardise the implant's stability. If excessive micromotion occurs, a fibrous capsule around the implant can form at the interface between the implant and periprosthetic bone; preventing osseointegration.[20,31] Traumatic fixture losses occurred at various time points after implantation.

The primary reason of BAHI losses was failure to osseointegrate; responsible for 74% of all implant losses. The fixture extrusion rate due to osseointegration failure was previously reported 1.3% to 3.4%; while the present review identified a higher occurrence rate of 5.3%. Osseointegration is a dynamic process that develops gradually following fixture implantation. The initial stability of the implant is mechanically initiated intra-operatively via the implant screw that is secured to the skull bone with precise torque parameters. Data pertaining to the timing of implant loss was not always reported in the included studies; the timing of only 61 out of the 217 implants lost due to failure of osseointegration was specifically mentioned. When available, data from included articles suggest that spontaneous extrusion of implants due to lack of osseointegration could occur at any moment following implantation. Included cohorts noticed early implant losses (within 6 months of implantation) occurring due to a lack of initial osseointegration. Also spontaneous losses occurred even years after implantation. This suggests that there could be a lack of initial skeletal fixation, but also a bio-structural change in the bone-implant interface that could occur even after a successful initial fixation. Several factors influencing early post-operative implant osseointegration have already been identified in the field of dentistry that are, to a certain

extent, translatable to the field of osseointegrated BAHIs. These include implant material biocompatibility, implant macrostructure and microstructure, surgical approach and surgeon's experience, bone characteristics, and loading conditions.[32,33] On the other hand, late implant losses are more frequently associated with patient-related factors. Identified factors include previous radiotherapy exposure to the temporoparietal skull, diabetes, smoking, alcohol abuse and various medication uses. There is biochemical and clinical evidence suggesting a relationship between the aforementioned and the impairment of bone metabolism, which could interfere with the osseointegration process.[34,35] For example, it is shown that heavy smokers have reduced bone mass compared with non-smoker.[36] Exposure to irradiation is known to have a negative effect on cranial blood flow, compromising osseointegration and affecting the survival of osseointegrated dental and craniofacial implants.[37-40] It is well known that an adequate blood supply is critical for proper bone healing and osseointegration.[41,42] There is also clinical evidence suggesting that BAHI loss is more common in irradiated bone.[43,44] Increased BAHI loss in diabetic patients has also been observed.[45,46] Diabetes animal models investigating implant osseointegration have demonstrated decreased bone formation and overall bone-to-implant contact, and the presence of woven bone instead of lamellar bone.[47-51] In clinical studies, type 2 diabetes patients have shown both decreased biochemical markers for bone formation and elevated markers for bone resorption, causing these patients to have altered bone remodeling affecting the osseointegration process.[52-56]

Despite the retrospective nature of most studies, included articles failed to consistently report important surgery and implant details such as abutment size, surgical approach, processor coupling time, anesthesia use and intraoperative findings. Recently improved surgical approaches and wider screws with roughened surfaces have allowed better osseointegration and implant stability resulting in lower implant failure rates.[9-11,57] Nonetheless, BAHI losses occurred in

cohorts published from 2001 to 2017. Although surgical approaches and implant characteristics have been enhanced, there was no trend in decreased losses in most recent publications. Moreover, most studies failed to mention if the patient presenting with a BAHI loss was taking medication. These factors have also been associated with BAHI loss and should be considered when investigating reasons behind implant loss. The primary limitation of our study is the fact that our main focus (BAHI loss) is rarely the primary outcome of the included studies. Therefore, specific patient information pertaining to those with BAHI losses is not always described.

CONCLUSION

BAHI losses are more common in pediatric recipients after traumatic events. Spontaneous implant losses due to failure to osseointegration can occur and suspected factors associated with these implant losses are highlighted in this review. These factors should be considered when assessing patients' candidacy and when investigating reasons for compromised implant stability or implant loss. Future studies are needed to bio-structurally investigate the mechanisms behind these factors that impede the integrity of the bone-implant interface.

ACKNOWLEDGMENTS

The authors would like to acknowledge Taline Ekmekjian and the staff at the McConnell Resource Centre of the McGill University Health Centre for creating the search strategies used in this systematic review.

REFERENCES

1. Tjellström A, Lindström J, Hallén O, Albrektsson T, Brånemark PI. Osseointegrated titanium implants in the temporal bone. A clinical study on bone-anchored hearing aids. Am J Otol 1981; 2: 304–10.
2. Dun CA, Faber HT, de Wolf MJ, Mylanus EA, Cremers CW, Hol MK. Assessment of more than 1,000 implanted percutaneous bone conduction devices: skin reactions and implant survival. Otol Neurotol. 2012, 33(2):192-8.
3. Tjellström A, Lindström J, Hallén O, Albrektsson T, Brånemark PI. Osseointegrated titanium implants in the temporal bone. A clinical study on bone-anchored hearing aids. Am J Otol 1981;2:304–10.
4. Den besten CA, Nelissen RC, Peer PG, et al. A Retrospective Cohort Study on the Influence of Comorbidity on Soft Tissue Reactions, Revision Surgery, and Implant Loss in Bone-anchored Hearing Implants. Otol Neurotol. 2015;36(5):812-8.
5. Wallberg E, Granström G, Tjellström A, Stalfors J. Implant survival rate in bone-anchored hearing aid users: long-term results. J Laryngol Otol. 2011;125(11):1131-5.
6. Horstink L, Faber HT, De wolf MJ, Dun CA, Cremers CW, Hol MK. Titanium fixtures for bone-conduction devices and the influence of type 2 diabetes mellitus. Otol Neurotol. 2012;33(6):1013-7.
7. Kiringoda R, Lustig LR. A meta-analysis of the complications associated with osseointegrated hearing aids. Otol Neurotol. 2013;34(5):790-4.
8. Larsson A, Tjellström A, Stalfors J. Implant losses for the bone-anchored hearing devices are more frequent in some patients. Otol Neurotol. 2015;36(2):336-40.

9. Johansson ML, Stokroos RJ, Banga R, et al. Short-term results from seventy-six patients receiving a bone-anchored hearing implant installed with a novel minimally invasive surgery technique. Clin Otolaryngol 2017 [epub ahead of print].
10. Verheij E, Bezdjian A, Grolman W, Thomeer HG. A systematic review on complications of tissue preservation surgical techniques in percutaneous bone conduction hearing devices. Otol Neurotol. 2016;37(7):829-37.
11. Shah FA, Johansson ML, Omar O, Simonsson H, Palmquist A, Thomsen P. Laser-modified surface enhances osseointegration and biomechanical anchorage of commercially pure titanium implants for bone-anchored hearing systems. PLoS ONE. 2016;11(6):e0157504.
12. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9, W64.
13. Mcdermott AL, Williams J, Kuo M, Reid A, Proops D. The birmingham pediatric bone-anchored hearing aid program: a 15-year experience. Otol Neurotol. 2009;30(2):178-83.
14. Granström G, Bergström K, Odersjö M, Tjellström A. Osseointegrated implants in children: experience from our first 100 patients. Otolaryngol Head Neck Surg. 2001;125(1):85-92.
15. De wolf MJ, Hol MK, Huygen PL, Mylanus EA, Cremers CW. Nijmegen results with application of a bone-anchored hearing aid in children: simplified surgical technique. Ann Otol Rhinol Laryngol. 2008;117(11):805-14.
16. Lloyd S, Almeyda J, Sirimanna KS, Albert DM, Bailey CM. Updated surgical experience with bone-anchored hearing aids in children. J Laryngol Otol. 2007;121(9):826-31.
17. Tietze L, Papsin B. Utilization of bone-anchored hearing aids in children. Int J Pediatr Otorhinolaryngol. 2001;58(1):75-80.

18. Drinias V, Granström, Tjellström A. High age at the time of implant installation is correlated with increased loss of osseointegrated implants in the temporal bone. Clin Implant Den Relat Res. 2007;9(2):94-9.
19. Willie BM, Yang X, Kelly NH, et al. Cancellous bone osseointegration is enhanced by in vivo loading. Tissue Eng Part C Methods. 2010;16(6):1399-406.
20. Pilliar RM, Lee JM, Maniatopoulos C. Observations on the effect of movement on bone ingrowth into poroussurfaced implants. Clin Orthop Relat Res. 1986;208:108.
21. Demontiero O, Vidal C, Duque G. Aging and bone loss: new insights for the clinician. Ther Adv Musculoskelet Dis. 2012;4(2):61-76.
22. Goldhahn J, Suhm N, Goldhahn S, Blauth M, Hanson B. Influence of osteoporosis on fracture fixation--a systematic literature review. Osteoporos Int. 2008;19(6):761-72.
23. Kim WY, Han CH, Park JI, Kim JY. Failure of intertrochanteric fracture fixation with a dynamic hip screw in relation to pre-operative fracture stability and osteoporosis. Int Orthop. 2001;25(6):360-2.
24. Apostu D, Lucaciu O, Berce C, Lucaciu D, Cosma D. Current methods of preventing aseptic loosening and improving osseointegration of titanium implants in cementless total hip arthroplasty: a review. J Int Med Res. 2017.
25. Chan GK, Duque G. Age-related bone loss: old bone, new facts. Gerontology. 2002;48(2):62-71.
26. Razi H, Birkhold AI, Weinkamer R, Duda GN, Willie BM, Checa S. Aging leads to a dysregulation in mechanically driven bone formation and resorption. J Bone Miner Res. 2015;30(10):1864-73.

27. Srunivasan S, Gross TS, Bain SD. Bone mechanotransduction may require augmentation in order to strengthen the senescent skeleton. Ageing Res Rev. 2012;11(3):353-60.

28. Mcdermott AL, Williams J, Kuo MJ, Reid AP, Proops DW. The role of bone anchored hearing aids in children with Down syndrome. Int J Pediatr Otorhinolaryngol. 2008;72(6):751-7

29. Marsella P, Scorpecci A, Pacifico C, Tieri L. Bone-anchored hearing aid (Baha) in patients with Treacher Collins syndrome: tips and pitfalls. Int J Pediatr Otorhinolaryngol. 2011;75(10):1308-12.

30. Doshi J, Mcdermott AL, Reid A, Proops D. The use of a bone-anchored hearing aid (Baha) in children with severe behavioural problems - the Birmingham Baha programme experience. Int J Pediatr Otorhinolaryngol. 2010;74(6):608-10.

31. Soballe K, Hansen ES, Rasmussen H, Jorgensen PH, Bunger C. Tissue ingrowth into titaniumand hydroxyapatitecoated implants during stable and unstable mechanical conditions. J Orthop Res 10, 285, 1992.

32. Bridges J, Bentler R. Relating hearing aid use to well-being among older adults. Hear J. 1998;51:39–44.

33. Marfatia H, Priya R, Sathe NU, Mishra S. Challenges during BAHA surgery: our experience. Indian J Otolaryngol Head Neck Surg. 2016;68(3):317-21.

34. Esposito M, Hirsch J, Lekholm U, Thomsen P. Differential diagnosis and treatment strategies for biologic complications and failing oral implants: a review of the literature. Int J Oral Maxillofac Implants. 1999;14(4):473-90.

35. Chrcanovic BR, Kisch J, Albrektsson T, Wennerberg A. Factors Influencing Early Dental Implant Failures. J Dent Res. 2016;95(9):995-1002.

36. Ward KD, Klesges RC. A meta-analysis of the effects of cigarette smoking on bone mineral density. Calcif Tissue Int. 2001;68(5):259-70.

37. Ihde S, Kopp S, Gundlach K, Konstantinović VS. Effects of radiation therapy on craniofacial and dental implants: a review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107(1):56-65.

38. Granström G. Osseointegration in irradiated cancer patients: an analysis with respect to implant failures. J Oral Maxillofac Surg. 2005;63(5):579-85.

39. Granström G. Radiotherapy, osseointegration and hyperbaric oxygen therapy. Periodontol 2000. 2003;33:145-62.

40. Granström G, Tjellström A, Albrektsson T. Postimplantation irradiation for head and neck cancer treatment. Int J Oral Maxillofac Implants. 1993;8(5):495-501.

41. McKibbin B. The biology of fracture healing in long bones. J Bone Joint Surg Br. 1978;60:150–162.

42. Street J, Bao M, deGuzman L, et al. Vascular endothelial growth factor stimulates bone repair by promoting angiogenesis and bone turnover. Proc Natl Acad Sci USA. 2002;99(15):9656-61.

43. Den besten CA, Stalfors J, Wigren S, et al. Stability, survival, and tolerability of an auditory osseointegrated implant for bone conduction hearing: long-term follow-up of a randomized controlled trial. Otol Neurotol. 2016;37(8):1077-83.

44. Calvo bodnia N, Foghsgaard S, Nue møller M, Cayé-thomasen P. Long-term results of 185 consecutive osseointegrated hearing device implantations: a comparison among children, adults, and elderly. Otol Neurotol. 2014;35(10):e301-6.

45. Nelissen RC, Stalfors J, De wolf MJ, et al. Long-term stability, survival, and tolerability of a novel osseointegrated implant for bone conduction hearing: 3-year data from a multicenter, randomized, controlled, clinical investigation. Otol Neurotol. 2014;35(8):1486-91.
46. Dun CA, De wolf MJ, Hol MK, et al. Stability, survival, and tolerability of a novel baha implant system: six-month data from a multicenter clinical investigation. Otol Neurotol. 2011;32(6):1001-7.
47. Siqueira JT, Cavalher-Machado SC, Rana-Chavez VE, et al. Bone formation around titanium implants in the rat tibia: role of insulin. Implant Dent. 2003;12:242-51.
48. Kwon PT, Rahman SS, Kim DM, et al. Maintenance of osseointegration utilizing insulin therapy in a diabetic rat model. J Periodontol. 2005;76:621-6.
49. Retzepi M, Donos N. The effect of diabetes mellitus on osseous healing. Clin Oral Implants Res. 2010;21:673-81.
50. Wang F, Song YL, Li DH, et al. Type 2 diabetes mellitus impairs bone healing of dental implants in GK rats. Diabetes Res Clin Pract. 2010;88:e7-e9.
51. Liu Z, Aronson J, Wahl EC, et al. A novel rat model for the study of deficits in bone formation in type-2 diabetes. Acta Orthop. 2007;78:46-55.
52. Cakatay U, Telci A, Kayali R, et al. Changes in bone turnover on deoxypyridinoline levels in diabetic patients. Diabetes Res Clin Pract. 1998;40:75Y9.
53. Rosato MT, Schneider SH, Shapses SA. Bone turnover and insulinlike growth factor I levels increase after improved glycemic control in noninsulin-dependent diabetes mellitus. Calcif Tissue Int. 1998;63:107-11.
54. Isaia GC, Ardissone P, Di SM, et al. Bone metabolism in type 2 diabetes mellitus. Acta Diabetol. 1999;36:35-8.

55. Cutrim DM, Pereira FA, de Paula FJ, et al. Lack of relationship between glycemic control and bone mineral density in type 2 diabetes mellitus. Braz J Med Biol Res. 2007;40:221-7.

56. Takizawa M, Suzuki K, Matsubayashi T, et al. Increased bone resorption may play a crucial role in the occurrence of osteopenia in patients with type 2 diabetes: Possible involvement of accelerated polyol pathway in its pathogenesis. Diabetes Res Clin Pract. 2008;82: 119-26.

57. Nelson KL, Cox MD, Richter GT, Dornhoffer JL. A comparative review of osseointegration failure between osseointegrated bone conduction device models in pediatric patients. Otol Neurotol. 2016;37(3):276-80.

LINKING STATEMENT

The article identified several factors that are associated with implant loss. These findings should be considered when assessing patients' candidacy or when investigating reasons for compromised implant stability or implant loss. The study shows that a subjective and quantifiable tool measuring the integrity and stability of the bone-implant interface is valuable as it could have important clinical relevance in the prevention of implant loss and also to determine when the bone-implant interface is sufficiently osseointegrated so it could carry the load bearing sound processor.

Intra-operative resonance frequency analysis determines processor coupling time in pediatric and adult bone-anchored hearing implant recipients

Aren Bezdjian, Rachel Ann Smith, Marco Bianchi, Bettina M. Willie, Sam J. Daniel

ABSTRACT

Objective: To investigate the use of peri-operative Resonance Frequency Analysis (RFA) measurements to indicate the optimal latency period prior to processor coupling in adult and pediatric patients.

Methods: A non-randomized prospective cohort study was conducted at the McGill University Health Centre. Patients were included if an intra-operative baseline RFA measurement and at least one follow up measurements were obtained. Patient age at implantation, indication for surgery, laterality of implantation, surgical approach, implant characteristics, skin tolerability, and stability measurements were gathered.

RESULTS: In total, 29 BAHIs were placed in 13 pediatric (mean age: 10.6, range: 5 – 17 years) and 16 adult (mean age: 45.9, range: 18 – 70) patients. The most common surgical approach for BAHI surgery in our cohort was the MIPS technique in 20 patients (5 pediatric) followed by implantation through linear incision in 9 patients (8 pediatric). There is an increase in stability quotient after implantation seen similarly in both cohorts. After 7 weeks of implantation, stability assessments regress to intra-operative scores in adults. However, a significant increase in stability quotients were found at the 3 to 6 weeks in the pediatric cohort.

Conclusion: Currently there is no standardized objective measurement of in vivo implant stability or consensus on the duration of the latency period, prior to processor coupling. Our clinical data show that 1) for pediatric patients, a 6-week latency period prior to coupling the sound processor is warranted. 2) For adults, processor coupling could likely be performed as soon as skin around the abutment site has healed. The non-invasive RFA method for measuring implant stability seems to have clinical relevance and could be an important tool added to BAHI surgery. Further clinical

and preclinical assessment is needed to understand what bone and patient specific factors influence the RFA measurement and its relationship with osseointegration.

INTRODUCTION

Since the late 70s, bone anchored hearing implants (BAHIs) have been successfully implanted to rehabilitate hearing-impaired individuals meeting eligibility criteria [1, 2]. The success of these implants heavily relies on the structural and mechanical integration of the implant surface in the surrounding bone, termed osseointegration [3].

The most commonly implanted BAHI is percutaneous in nature, and has seen many enhancements since the first reported case [4]. These include improved surgical approaches successfully decreasing operative time and peri-operative complications, and implant design improvements such as wider screws with roughened surfaces that better implant stability, resulting in fewer implant failure rates [5-9]. Although the long-term success rate is high and most adverse events occurring with BAHIs are related to skin tolerability, implant losses do occur. A recent systematic review estimates that 7.1% of all BAHIs placed are lost [10]. The review also indicates that spontaneous implant extrusion due to failure of osseointegration is the primary reason of BAHI losses accounting for 74% of all reported losses. Moreover, this type of implant loss could occur spontaneously at any time after placement [10].

Our implant center at the McGill University Health Centre has adopted a single stage procedure where the BAHI screw and abutment are installed in a single operative procedure in both adult and pediatric patients. Surgical installation of the implant screw and abutment is followed by a latency period before the sound processor can be coupled. The aim of this latency period is to ensure sufficient osseointegration and subsequent implant stability by limiting micromotion at the bone-implant interface. Limited preclinical or clinical data is available to support the duration and efficacy of such a latency period for auditory implants. Nonetheless, it is well-established that early coupling is strongly warranted to minimize the detrimental period of

auditory deprivation, particularly in children. Based on this concern and previous reports, our center has adopted a mandatory latency period of over 6 weeks prior to processor coupling [11, 12].

The lack of consensus or clear indicator of the optimal latency period prior to processor coupling for BAHIs is mainly due to a paucity of clinical data since there is no standard tool to evaluate the in vivo stability of the bone-implant interface. The use of Resonance Frequency Analysis (RFA) has recently been introduced to measure the initial stability of dental and orthopedic implants [13]. This non-invasive tool has also attracted the attention of researchers in the field of auditory osseointegrated implants [14]. The advent of an implant stability measurement tool in BAHI practice such as the RFA could not only indicate the optimal coupling time of the sound processor for each patient, but could also predict and prevent implant loss due to impeded stability.

This prospective cohort study investigates the use of peri-operative RFA measurements to indicate the optimal latency period prior to processor coupling in adult and pediatric patients.

METHODS

Study Design

This prospective cohort study received McGill University Health Centre Research Ethics Board approval. All patients undergoing BAHI surgery at our tertiary implant center from January 2015 until April 2017 with intra-operative and at least one follow up stability score were included. The post-operative follow up period for the study ended in March 2018.

The primary outcomes evaluated the progression of RFA in pediatric and adult implant cohorts. Extracted data included patient age at implantation, indication for surgery, laterality of

implantation, surgical approach, implant characteristics, skin tolerability assessed and classified according to the Holgers classification, and stability measurements.

Surgical Intervention

All implantations were performed in a single-stage surgical procedure by the same surgeon (S.J.D.) by either a linear incision approach or Minimally Invasive Ponto Surgery (MIPS). Surgical approach and local anesthesia benefits were discussed and a joint decision between the surgeon, patient and/or parent was reached. After a minimum of six weeks, the decision to load the implant was made by the surgeon based on a subjective clinical assessment of the implant site. This assessment encompassed the RFA stability measure, the integrity of the soft tissue status surrounding the implant site, and a consensus between the patient and/or parent, audiologist and the surgeon.

Linear incision technique without subcutaneous tissue reduction

Since 2010, several groups have reported improved tolerance to percutaneous devices implanted without reduction of the soft tissue surrounding the percutaneous abutment [6]. Therefore, implantation through linear incision without soft tissue reduction as described by Hultcrantz was performed [7]. During this technique, subcutaneous tissue is dissected prior to the exposure and mobilization of the periosteum. This was followed by the drilling procedure with saline irrigation for cooling as described by Tjellstrom and Granstrom [4]. Finally, a hole is punched through the skin above the linear incision, in order to externalize the abutment.

Minimally Invasive Ponto Surgery (MIPS)

MIPS is a minimally invasive approach described by Oticon Medical in 2015 aimed to optimize tissue preservation with specialized surgical components [15]. For the MIPS procedure,

the position of the implant is determined using the sound processor indicator. The skin thickness is measured, and a 5 mm circular incision punch was made, with the bone exposed using a double-ended dissector. Drilling is performed with copious cold saline irrigation to prevent heat-induced trauma. No linear incision or flap is needed since drilling is performed with a cannula guided drilling system. The abutment is then inserted and, if necessary, manually tightened.

Implant Stability Measures

Traditionally, commercially available systems that uses an impact percussion technique to assess the interface of natural teeth such as the Periotests (Medizintechnik Gulden, Modautal, Germany) have been proposed to evaluate the stability of osseointegrated auditory implants [16]. However, these systems have been applied to the auditory field with limited success primarily because osseointegrated implants are considerably stiffer than natural teeth.

Resonance frequency analysis (RFA) was introduced by Meredith et al. to clinically test implant dental and orthopedic stability in a non-destructive manner [13]. A small aluminium rod (SmartPeg) is attached to the abutment with a screw connection and is thereafter stimulated by magnetic pulses from a handheld electronic device. The instrument measures the resulting resonance frequency (in Hz) and translates this into a more clinically useful implant stability quotient (ISQ) scale. The ISQ scales ranges from 1 to 100; the higher the ISQ, the more stable the implant. Measurements are conducted in 2 perpendicular directions resulting in two different ISQ values: ISQ high and ISQ low.

ISQ scores were used to display overall mean progression or regression of implant stability and to allow comparison of obtained scores between pediatric and adult patients. However, it is known that implant geometry (i.e. diameter, thread profile) and drilling protocol, as well as abutment length and status of skin surrounding the implant are factors that could potentially

influence the RFA measurement [9, 14, 17]. For these reasons, threshold shifts (difference from baseline within a patient) were used to monitor the development of implant stability as they hold constant implant related influencing factors. These threshold shifts were evaluated at each follow up visit. When multiple follow up scores were obtained for a patient in the same time period, the more recent score was used. All included patients in this study had intra-operative and at least one post-operative measurement assessing implant stability.

Statistics

Comparisons of mean ISQ values were done with independent sample t-test. An average of ISQ values during the period from baseline (time of implantation) to 15 weeks follow-up were obtained. The threshold shifts were defined as the difference between the intra-operatively obtained measurement and the follow up scores. Standard errors of means were used to create error bars on figures illustrating ISQ scores between groups.

Fisher's test analysis was conducted for the comparison of Holgers scores between groups. A correction factor was developed and validated in reference material by Osstell (Osstell, Goteborg, Sweden) to correct ISQ values. Only these corrected data are presented throughout the study.

RESULTS

Patient Characteristic

Twenty-nine patients were included in the study. Thirteen patients were pediatric (<18 years old) and 16 patients were adults (Table 1). Mean age at surgery was 30.1 years for the entire cohort, 10.6 years for the pediatric cohort (Median: 12 years; Range: 5 - 17) and 45.9 years for the adult cohort (Median: 49 years; Range: 18 - 70). All implants were placed unilaterally; 17 on the right and 12 on the left side.

The most common diagnosis for BAHI candidacy was conductive hearing loss observed in 13 patients; 8 of which were caused by aural atresia. Sensorineural hearing loss was present in 6 BAHI recipients, 3 patients acquired hearing loss due to acoustic neuroma and 7 had other conditions such as Meniere's disease and Cogan's syndrome.

Table 1. Patient Characteristics

Characteristic	**n**	**Mean**	**Median**	**Range**
Age at surgery (in years)				
Pediatric	13	10.6	12	5 – 17
Adult	16	45.9	49	18 – 70
Total cohort	29	30.1	19	5 – 70
Etiology of hearing loss				
Conductive	13			
SNHL	6			
Post acoustic neuroma	3			
Others	7			
Laterality *(all unilateral)*				
Right	17			
Left	12			

Implants and Surgical Intervention

All patients drilled with 4 mm countersink and widening drill and all patients were implanted with 4 mm screw diameters. Abutment lengths were determined by measuring skin thickness. These were 6 mm in 1 patient, 9 mm for 18 patients, 12 mm for 8 patients and 14 mm for 2 patients (Table 2). The most common surgical approach for BAHI surgery in our cohort was the MIPS technique in 20 patients (5 pediatric; 15 adult) followed by implantation through linear

incision in 9 patients (8 pediatric; 1 adult). One adult patient underwent implantation through the linear incision with tissue reduction due to a high body mass index.

Table 2. Surgical and implant characteristics

Characteristic	Pediatric (n)	Adult (n)	Total (n)
Surgical Approach			
MIPS	5	15	20
Linear	8	1	9
Abutment Length *			
6mm	1	0	1
9mm	9	9	18
12mm	2	6	8
14mm	1	1	2
ISQ Follow Up			
Intra-operative	13	16	29
<1 week	12	12	24
1-2 weeks	11	14	25
3-6 weeks	11	13	24
7-15 weeks	7	6	13

* screw diameter 4mm for all implants placed

Implant Stability Quotient

The number of patients followed via ISQ scores at each time point is tabulated in Table 2. Low and High ISQ scores in adults were significantly greater at all time points measured compared to pediatric patients (Figure 1).

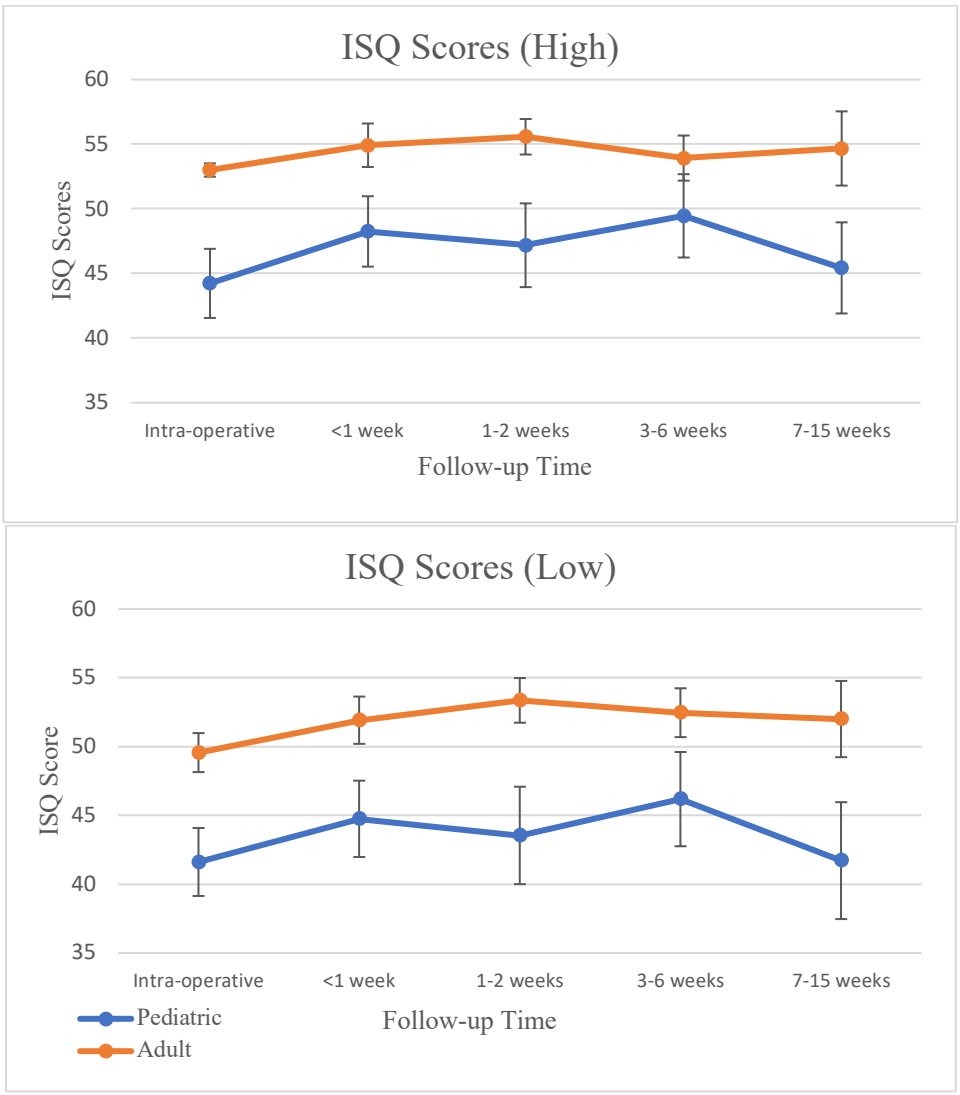

Figure 1. Mean implant stability values of pediatric and adult BAHI recipients at various timepoints as assessed by the ISQ score. Average values of all participants presented. Error bars indicate standard error of the mean.

ISQ values displayed as threshold shifts from the intra-operative baseline score are graphed in Figure 2. There is a significant increase in threshold shift after implantation seen similarly in both adult and pediatric cohorts. In adults, threshold shifts regress to intra-operative scores at 3 to 6 weeks (High) and at 7 to 15 weeks follow up (High and Low). Children have significantly increased ISQ thresholds throughout long-term stability assessment. Pediatric threshold shifts are

significantly higher than the adult cohort at 3 to 6 weeks follow up (High) and at the 7 to 15 weeks follow up (High and Low).

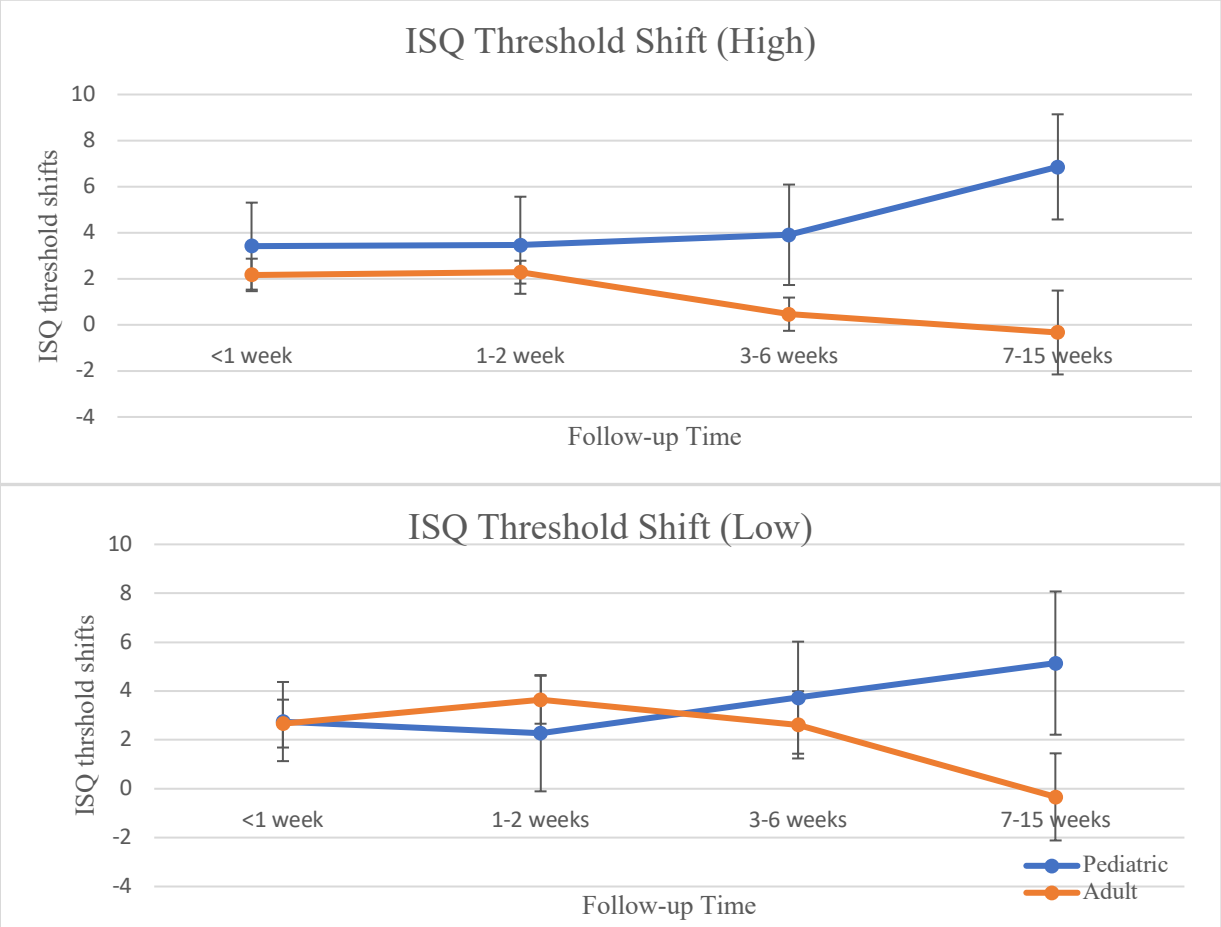

Figure 2. Mean implant stability threshold shifts of pediatric and adults BAHI recipients at various timepoints as assessed by the ISQ score. Average values over all participants. Error bars indicate standard error of the mean.

Skin tolerability

An exact Fisher's analysis comparing skin tolerability observations between groups reveal that pediatric recipients had significantly more adverse skin reactions compared to adults (p-value = 0.05). Pediatric patients presented with 22 Grade I reactions, 13 Grade II reactions and 2 Grade

III reactions at follow up visits, while adults had 17 Grade I reactions and 2 Grade II reactions (Table 3).

Table 3. Skin reaction incidences using Holgers classification observed

Holgers Classification	*Pediatric (n)*	*Adults (n)*	*p **
***Grade 1**: light redness and slight swelling*	22	17	0.05
***Grade 2**: redness and swelling*	13	2	
***Grade 3**: redness, swelling, moistness, and slight granulation tissue*	2	0	
***Grade 4**: redness, swelling, moistness, granulation tissue, and infection*	0	0	

n = number of observations
* p-value calculated by exact Fisher's showing that pediatric patients presented more overall skin reaction

DISCUSSION

The latest consensus as to when to couple the BAHI sound processor dates from 2005 and advocates for a post-operative 4 to 6 weeks waiting period post-implantation [12]. However, this consensus was based on limited experimental or clinical evidence. Additionally, surgical innovations and developments in implant designs claim to ensure better initial stability and later, osseointegration. Thus, the trends in early coupling of the sound processors is increasingly sought out. Data from the dental field shows that implants may be successfully loaded before osseointegration is complete as long as good primary stability is maintained [18].

Summarized in Table 4 are a subset of clinical data that have successfully adopted earlier processor coupling protocols for osseointegrated auditory implants in pediatric and adult patients. Hogsbro et al. safely coupled the sound processor 1 week after surgery for adult patients with

expected normal bone quality and no conflicting skin condition [19]. These studies highlight the possibility that micromotions from the sound processor are negligible and do not affect osseointegration.

Table 4. Selected studies adopting standardized early sound processor loading time

Article	Type of Study	Loading Time	Patient Info	Implant losses	Follow-up Time	Study Conclusion	ISQ scores included?
D'Eredita et al 2012	*Prospective cohort study*	3 weeks	12 patients (3 children, 9 adults)	None	1 year	Implants can be safely loaded at 3 weeks	Yes
Hogsbro et al 2015	*Randomized, non-blinded study*	2 weeks	47 adult patients	None	1 year	Implants can be safely loaded at 2 weeks	Yes
Hogsbro et al 2017	*Prospective cohort study*	1 week	25 adult patients Mean age: 57.4 years	None	1 year	Implants can be safely loaded at 1 week	Yes
McLarnon et al 2012	*Prospective cohort study*	4 weeks	68 patients	None	16 weeks	Implants can be safely loaded at 4 weeks	Yes
Nelissen et al 2016	*Prospective cohort study*	3 weeks	30 adult patients	1 implant loss in a 65-year-old man at 3 days post implantation	3 years	Implants can be safely loaded at 3 weeks	Yes ISQ at the time of implant surgery was 44.
Wazen et al 2015	*Prospective cohort study*	3 weeks	20 adult patients	None	1 year	Implants can be safely loaded at 3 weeks	Yes

In our prospective cohort, implant design differences were negligible. Implant screw diameters were 4 mm for all implants placed in our cohort and the most common abutment lengths for both cohorts were 9 mm. However, almost all adult recipients underwent implantation through the MIPS technique while the majority of pediatric patients received their implants via the linear incision approach. This difference in techniques between cohorts is largely due to the fact that during that time period, MIPS implantations at our institution were only being performed in patients over 14 years of age, when the bone has achieved a sufficient thickness. Our prospective

cohort comparing age-related stability trends displayed overall lower stability quotient scores in pediatric patients when compared to adults. However, difference in these raw ISQ scores could be attributed to differing surgical techniques and varying abutment lengths [5, 17].

It is important to note that there is no consensus as to how the RFA-derived ISQ score directly measures osseointegration. ISQ score is primarily based on physical properties supporting that resonance frequency measures will increase when stabilizing forces around the implant are increased [14]. These interface strength between the implant and bone is likely to influenced by several implant-specific factors including implant geometry, diameter, thread profile, and abutment length and as well as surgical and patient-related factors such as drilling protocol (i.e. insertion depth, angulation) and status of skin surrounding the implant and bone quality. For these reasons, stability threshold shifts in BAHI recipients are more effective when monitoring the development of implant stability as they are largely independent of implant-, surgical- and patient-related influencing factors.

In our cohort, this analysis showed that while both pediatric and adult patients had an increase in stability quotients in the first 2 weeks post-operatively, the adult stability measurements regressed to the baseline values at later follow up time points. However, this was not the case in pediatric patients; a significant and permanent stability quotient increase occurred after 3 to 6 weeks post-operatively when compared to intra-operative baseline measurements.

It has been suggested that pediatric and adult cohorts have different osseointegration trends, although the possible cellular mechanisms behind this difference in bone biology is not clearly elucidated [20]. Also, there is limited data comparing bone material properties and microstructure of a child's temporal bone from that of an adult. Overall bone mineral density in the temporal bone is generally low at birth and increases with age and as a result likely influences osseointegration.

Bone density development parallels the increase in head circumference as well as increase in the skull breadth, length, and height [21, 22]. A study assessing age-related differences in the organization of pneumatized spaces in the temporal bone used high-resolution computed tomography scans to demonstrate age-specific patterns of ontogenetic changes which may contribute to differences in osseointegration [23]. Also associated with bone-implant interface strength are the air cells generally filled with bone marrow cells and the more extended blood supply in the pediatric skull bone [24].

A challenge presenting in BAHI surgery and stability is when bone thickness is insufficient, and/or the skull surface is irregular, which is commonly seen in syndromic patients such Treacher Collins syndrome [25]. Cone beam computed tomography of the skull is performed at some implant centers to assess cortical bone thickness as well as provide volumetric bone mineral density prior to surgery for syndromic patients [25].

The temporal bone material properties are likely to influence the required latency period, since the processor coupling results in loading and micromotion of the bone-implant interface. Preclinical studies in long bones have demonstrated that there is an optimal magnitude and duration of loading to enhance healing while avoiding excessive micromotion. This leads to fibrous tissue formation which impedes osseointegration [26, 27]. Preclinical studies are needed in the temporal bone to determine if a longer latency period and delay in processor coupling is beneficial to reach optimal osseointegration.

Implant fixture loss did not occur in our cohort. Therefore, our cohort did not permit the evaluation of ISQ trends in cases of implant loss. It is expected however, that if ISQ scores are significantly reduced post-operatively, the processor coupling could be delayed or halted to permit enhanced osseointegration uninterruptedly and thereby prevent implant extrusion. There are

however studies in the dental field where ISQ failed to indicate subsequent implant loss [28]. It is therefore thought that paradigm of factors can be influencers of implant extrusion.

Inadequate post-operative hygienic care increases the risk of implant site infections and as a result, is attributed to a higher skin reaction incidence as observed in our pediatric patients [2, 29].

Conclusion

The analysis of our cohort aimed to identify an optimal latency period prior to processor coupling for pediatric and adult BAHI recipients. Our findings advocate for different latency periods for both cohorts. For pediatric patients, a post-operative 6 weeks period should be accorded prior to coupling to reach an initial stability. For adults, the development from intra-operative baseline measurements is negligible, thus, processor coupling time could likely be performed as soon as skin around the abutment site has healed.

Limitation

A limitation of our study was the varying surgical approaches in the pediatric and adult patients as MIPS implantations are only offered for patients above the age of 14 years. The threshold shift analysis, however, should eliminate surgical differences. Our results are not influenced by surgeon's skills and experience as the same surgeon did all of the surgeries performed. While the follow up analysis was limited to 15 weeks, it would be beneficial to continue collecting data prospectively to identify long-term stability trends and to include more patients in later time points. Long term studies demonstrate a high ISQ value up to 36 months after surgery [9, 19].

CONCLUSION

Currently there is no standardized objective measurement of in vivo implant stability or consensus on the duration of the latency period, prior to processor coupling. Our clinical data show that 1) for pediatric patients, a 6-week latency period prior to coupling the sound processor is warranted. 2) For adults, processor coupling could likely be performed as soon as skin around the abutment site has healed. The non-invasive ISQ method for measuring implant stability has clinical relevance and could be an important tool added to BAHI surgery. While these data are promising, further clinical and preclinical assessment is needed to understand what bone and patient specific factors influence the RFA measurement and its relationship with osseointegration.

REFERENCES

1. Edmiston RC, Aggarwal R, Green KM. Bone conduction implants - a rapidly developing field. *J Laryngol Otol*. 2015;129(10):936-940.
2. Dun CA, Faber HT, de Wolf MJ, Mylanus EA, Cremers CW, Hol MK. Assessment of more than 1,000 implanted percutaneous bone conduction devices: skin reactions and implant survival. *Otol Neurotol*. 2012;33(2):192-198.
3. Brånemark PI. Osseointegration and its experimental background. *J Prosthet Dent*. 1983;50(3):399–410.
4. Tjellström A, Lindström J, Hallén O, Albrektsson T, Brånemark PI. Osseointegrated titanium implants in the temporal bone. A clinical study on bone-anchored hearing aids. *Am J Oto*l. 1981;2:304–310.
5. Johansson ML, Stokroos RJ, Banga R, et al. Short-term results from seventy-six patients receiving a bone-anchored hearing implant installed with a novel minimally invasive surgery technique. *Clin Otolaryngol*. 2017;42(5):1043-8.
6. Verheij E, Bezdjian A, Grolman W, Thomeer HG. A systematic review on complications of tissue preservation surgical techniques in percutaneous bone conduction hearing devices. *Otol Neurotol*. 2016;37(7):829-37.
7. Hultcrantz M, Lanis A. A five-year follow-up on the osseointegration of bone-anchored hearing device implantation without tissue reduction. *Otol Neurotol*. 2014;35(8):1480-5.
8. Shah FA, Johansson ML, Omar O, Simonsson H, Palmquist A, Thomsen P. Laser-modified surface enhances osseointegration and biomechanical anchorage of commercially pure titanium implants for bone-anchored hearing systems. *PLoS ONE*. 2016;11(6):e0157504.

9. Kruyt IJ, Banga R, Banerjee A, Mylanus EAM, Hol MKS. Clinical evaluation of a new laser-ablated titanium implant for bone-anchored hearing in 34 patients: 1-year experience. *Clin Otolaryngol*. 2018;43(2):761-764.

10. Bezdjian A, Smith RA, Willie B, Thomeer HGXM, Willie BM, Daniel SJ. A systematic review on factors associated with percutaneous bone anchored hearing implant loss. *Otol Neurotol.* 2018;[Epub ahead of print].

11. Tjellström A, Granström G. One-stage procedure to establish osseointegration: a zero to five years follow-up report. *J Laryngol Otol*. 1995;109:593–598.

12. Snik AFM, Mylanus EAM, Proops DW et al. Consensus statements on the BAHA system: where do we stand at present? *Ann Otol Rhinol Laryngol*. 2005;114(195):1–12.

13. Meredith N. Assessment of implant stability as a prognostic determinant. *Int J Prosthodont*. 1998;11:491–501.

14. Nelissen RC, Wigren S, Flynn MC, Meijer GJ, Mylanus EA, Hol MK. Application and interpretation of resonance frequency analysis in auditory osseointegrated implants: A review of literature and establishment of practical recommendations. *Otol Neurotol*. 2015;36:1518-1524.

15. Johansson M, Holmberg M. Design and clinical evaluation of MIPS- A new perspective on tissue preservation. Retrieved from https://www.oticonmedical.com.

16. Lukas D, Schulte W. Periotest – a dynamic procedure for the diagnosis of the human periodontium. *Clin Phys Physiol Meas.* 1990;11(1):65–75.

17. Calon TGA, Johansson ML, de Bruin AJG, et al. Minimally invasive ponto surgery versus the linear incision technique with soft tissue preservation for bone conduction hearing implants: A multicenter randomized controlled trial. *Otol Neurotol.* 2018;39(7):882-893.

18. Gapski R, Wang HL, Mascarenhas P, Lang NP. Critical review of immediate implant loading. *Clin Oral Implants Res*. 2003;14(5):515–527.

19. Hogsbro M, Agger A, Johansen LV. Successful loading of a bone-anchored hearing implant at 1 week after surgery. *Otol Neurotol*. 2017;38(2):207-211.

20. Lloyd S, Almeyda J, Sirimanna KS, Albert DM, Bailey CM. Updated surgical experience with bone-anchored hearing aids in children. *J Laryng Otol*. 2007;121(9):826-831.

21. Delye H, Clijmans T, Mommaerts MY, Sloten JV, Goffin J. Creating a normative database of age-specific 3D geometrical data, bone density, and bone thickness of the developing skull: a pilot study. *J Neurosurg Pediatr*. 2015;16:687–702.

22. Takahashi K, Morita Y, Ohshima S, Izumi S, Kubota Y, Horii A. Bone density development of the temporal bone assessed by computed tomography. *Otol Neurotol*. 2017;38:1445–1449.

23. Hill CA. Ontogenetic change in temporal bone pneumatization in humans. *Anatomical record* (Hoboken, NJ : 2007). 2011;294(7):1103-1115.

24. Drinias V, Granström, Tjellström A. High age at the time of implant installation is correlated with increased loss of osseointegrated implants in the temporal bone. *Clin Implant Den Relat Res*. 2007;9(2):94-99.

25. Marsella P, Scorpecci A, Pacifico C, Tieri L. Bone-anchored hearing aid (Baha) in patients with Treacher Collins syndrome: tips and pitfalls. *Int J Pediatr Otorhinolaryngol*. 2011;75(10):1308-1312.

26. Pilliar RM, Lee JM, Maniatopoulos C. Observations on the effect of movement on bone ingrowth into porous surfaced implants. *Clin Orthop Relat Res*. 1986;208:108.

27. Willie BM, Yang X, Kelly NH, et al. Cancellous bone osseointegration is enhanced by in vivo loading. *Tissue Eng Part C Methods*. 2010;16(6):1399-1406.

28. Sayardoust S, Omar O, Thomsen P. Gene expression in peri-implant crevicular fluid of smokers and nonsmokers. 1. The early phase of osseointegration. *Clin Implant Dent Relat Res*. 2017;19(4):681-693.

29. Kiringoda R, Lustig LR. A meta-analysis of the complications associated with osseointegrated hearing aids. *Otol Neurotol*. 2013;34(5):790-794.

LINKING STATEMENT

The study demonstrates differences in pediatric and adult bone-implant fixation. These are important when evaluating when to couple the external sound processor to the percutaneous implant. The findings of the study, although promising for clinical relevance, do not answer what the tested tool, RFA is actually measuring. Therefore, preclinical assessment is needed to understand what bone and patient specific factors influence these measurements and its relationship with stability. Thus, the next study was conducted with aims to further knowledge on the bone characteristics that are associated with better stability.

Age-related changes in temporoparietal bone material properties influence stability of bone-anchored hearing implants

Aren Bezdjian, Samer Salameh, Alice Bouchard, Maximilian Rummler, Sam J Daniel, Elizabeth Zimmermann, Bettina M. Willie

ABSTRACT

Research investigating the anchorage of the bone-implant interface is most often conducted in the fields of dentistry and orthopaedics. Little is known about the calvaria acting as a host bone for implants, as seen in osseointegrated bone anchored hearing systems. The present study investigates the relationship between primary stability as determined by the Resonance Frequency Analysis (RFA) tool, mechanical testing and calvaria characteristics in a human cadaveric model. 29 donated cadaveric skull bones were dissected to obtain the temporoparietal region where osseointegrated bone-anchored hearing implants (BAHIs) are placed. After placement, implant stability quotient was measured and repeated for precision testing. This stability quotient was correlated with mechanical testing outcomes (push-out test and fracture toughness tests). Finally, micro-CT imaging was performed in order to further investigate the properties of the host-bone receiving the implant. Donor characteristics indicate a relatively old average age of donor (mean = 76.8) as well as the presence of respiratory, cardiac, renal, neoplastic, and mixed comorbidities. Regression analysis of cadaveric implant properties showed a positive relationship between peak load and mean ISQ scores, between peak load and age of donor, and between crack growth toughness and age of donor. Furthermore, a negative relationship was found between crack initiation toughness and age of donor, and a non-linear relationship was observed between mean ISQ scores and age of donor. Our cadaveric data demonstrate that the RFA system accurately predicts the force required to displace the implant, suggesting that the non-invasive ISQ method for measuring implant stability has clinical relevance and could be an important tool added to BAHI surgery. However, the added value of the RFA system needs to be further investigated in younger bone samples and in in-vivo models to assess its relation with osseointegration

BACKGROUND

In the past two decades, bone anchored hearing implants (BAHIs) inserted in the temporal bone have rehabilitated hearing-impaired individuals with success rates of 90% or higher (Dun et al., 2012). These implantable devices primarily rely on two principles: 1) osseointegration; the direct structural and functional connection between the implant and the "living" bone, and 2) bone conduction hearing; the body's natural ability to transfer sound vibrations through the skull bone to be sensed by the inner ear, bypassing the outer and middle ear.

These devices successfully rehabilitate those suffering with conductive hearing loss secondary to congenital ear deformities (Grantröm et al., 2001). Current recommendations for the location of the BAHA implant, call for placement approximately 5 to 7 cm posterosuperior to the external auditory canal (EAC). This allows for a margin of safety to avoid the auricle, as well as the sigmoid sinus, when placing the implant in the calvarium. One of the major concerns when implanting BAHIs is the thickness and surface irregularities of the temporal bone at the implant site (Papsin et al., 1997). Nonetheless, it is uncommon to perform CT scans of an individual prior to implantation to determine skull thickness and regularity.

Although most adverse events associated with the percutaneous BAHI are skin-related (i.e. erythema, granulation tissue, inflammation, infection), implant loosening and extrusion can also occur, sometimes without any known cause (Den Besten et al., 2015; Bezdjian et al., 2019). Despite the overall low incidence of implant losses, there is a need to understand the underlying mechanisms leading to implant loss particularly in regard to primary stability failure. It remains unclear how much the quality and quantity of the host bone at the temporal site affects the stability of BAHIs.

A recent review identified that the primary reason of BAHI losses was failure to

osseointegrate, responsible for 74% of all implant losses (Bezdjian et al., 2019). Osseointegration is a dynamic process that develops gradually following fixture implantation. The initial stability of the implant is mechanically initiated intra-operatively when the implant screw is secured to the calvaria with precise torque parameters. Spontaneous losses can occur even years after implantation (Bezdjian et al., 2019). This suggests that there could be a lack of initial skeletal fixation, but also a biostructural change in the bone–implant interface that could occur even after a successful initial fixation.

The overall strength of the bone-implant contact is considered as: 1) the surgical fixation of the implant and its components (i.e., implant geometry, implant length and diameter, thread profile), and the drilling protocol used; 2) the extent of osseointegration (i.e., the amount of bone to implant contact); and 3) the characteristics of the surrounding tissues, determined by the trabecular-cortical bone ratio and the bone density (Meredith et al., 1998; Nelissen et al., 2015). Recently, resonance frequency analysis (RFA) is being used to clinically test the stability of auditory implants in a non-invasive manner. Most of what is known on implant stability as measured by RFA was discovered in research on dental and orthopedic implants.

Although little is known about the calvaria, it is clear in other anatomical sites that the bone quality and osseointegration capacity is related to age and co-morbidity which affect the individual's healing capacity (McLarnon et al., 2012). Age as a prognostic factor in dental implant success has been discussed by several authors. Older patients, theoretically, have potentially longer healing times, more systemic health factors, and the likelihood of poorer local bone conditions (Wood & Wermilyea, 2004). Similarly, aging and the reduction in fracture toughness has been identified in dentistry (Nazari et al., 2009).

Previous research examining joint replacements have shown that the dynamic process of

osseointegration is dependent on implant characteristics (i.e. pore diameter, surface), but less is known concerning the role of host bone quality. We hypothesized that age would have a significant effect on bone microstructure and mechanical properties (i.e. fracture toughness) and subsequent BAHI stability. This study investigates the relationship between calvaria bone quality, donor age, primary stability, mechanical testing in a human cadaveric model.

MATERIALS AND METHODS

Sawbone

A study evaluating the elastic modulus, tensile and flexural strength of various skull-simulate materials concludes that epoxy resin is a suitable model to replicate the human skull bone (Falland-Cheung et al., 2017). This artificial bone most allows for adequate structural testing of fixation of implants to the cortical bone. Short fiber filled epoxy sheets (Sawbones®, USA) were used. Implants were placed in two types of specialized Sawbone^{R} epoxy sheets: 1) replicating human skull bone, and 2) replicating compromised osteoporotic bone.

Human cadaveric donor bone

The temporoparietal skull bone region of donor cadaveric specimens were obtained for research. Samples were handled according to institutional and legislative regulations on research on cadaveric specimen. This study was performed with approval from the McGill University Health Centre Research Ethics Board (ref # A08-M31-18B) in accordance with Articles 2.9 and 6.12 of the Canadian Tri-Council Policy statement of Ethical Conduct for Research Involving Humans. Samples were transported by a specializd funeral home service. At the end of experiment, all samples were returned to be buried as per regulatory protocol. The specimens used for this

research project were derived from cadavers that were embalmed with standard formaldehyde-based containing: Ethanol 70%, Glycerin 20%, Formaldehyde 1.85%, Phenol 4.45%.

Implant characteristic and installation

Prior to implant placement, cadaveric samples were cut 50–55 mm from the ear canal at the top of the pinna. Anatomical landmarks, such as the zygomatic line, were used as guides. The samples were cut approximately 5cm x 5cm. Periosteum was removed above and under the samples. Installation of Oticon Ponto BHX 4 mm wide implants mounted with 6 or 9 mm abutments (Oticon Medical AB, Askim, Sweden) for all cadaveric experiments was conducted. A surgical drill with the guide drill was applied to the bone controlled by a pedal. A drill speed of 2000 rpm was applied. While drilling, only vertical drill motions of the burr were performed to ensure visual inspection and to avoid overheating by continuous and generous irrigation. A widening drill was applied to create a countersink in the bone. To install the implant, an abutment inserter was used to pick up the implant and torque limit of 40 Ncm low-speed was set. When the implant engaged the bone, the number of turns was counted. To ensure full installment, manual insertion was conducted until the final thread was submerged into the bone.

Resonance frequency analysis and implant stability quotient

A small titanium rod (Osstell AB, Göteborg, Sweden) containing a magnet stimulates a range of sound frequencies with subsequent measurement of vibratory oscillation of the implant. The instrument measures the resulting resonance frequency (in Hz) and translates it into the more clinically useful implant stability quotient (ISQ) scale, which ranges from 1 to 100. The higher the ISQ, the more stable the implant. Measurements are conducted in 2 perpendicular directions resulting in a high and low ISQ value. Measurements were recorded immediately after

implantation, and again 3 to 5 days after implantation. Threshold shifts were used to monitor implant stability as they hold constant implant related influencing factors.

Short term reproducibility of ISQ measurements

Assessment of precision errors were conducted to discover the short-term reproducibility of the ISQ measurement. In concordance to the methods described by Glüer et al. (1995), we calculated short-term precision errors using the root-mean-square (RMS) averages of standard deviations of repeated measurements (SD) and standard errors of the estimate of changes with time (SEE). Calculation of confidence intervals of precision errors were based on the number of repeated measurements and the number of subjects to serve as characterize limitations of precision error assessments.

$$SD_j = \sqrt{\sum_{i=1}^{n_j} \frac{(x_{ij} - \bar{x}_j)^2}{n_j - 1}}$$

where n_j is the number of measurements performed, x_{ij} is the result of the initial measurement for subject j, and x_j second measurements. Since the true mean of the measurement is unknown and has to be estimated from the mean of the n repeated measurements the denominator has to be represented as $(n_j - 1)$ in order to make SD^2 an unbiased estimate of the Gaussian probability distribution.

For the study, measurements performed in Sawbone, cadaver and humans were gathered. The nature of the ISQ is to gather two repeated measurements per time point in order to have and ISQ high and an ISQ low score. The precision error analysis investigated the discrepancies between measurements one (M_1) and measurements two (M_2) over a wide range of gather data. In

theory, these two scores must be similar to one another as they measure the same implant during the same time points. Average time between the two measurements in from 5 to 20 seconds.

Pushout test

The pushout mechanical test was performed in 20 cadaveric samples with a 4mm wide implant installed to measure the force required to displace the fixed implant. All implants had a 6mm abutment placed. The bone piece with the implant secured were transfer in a sterile urine sample cup where self-curing acrylic resin was poured (Ortho-Jet Powder & Liquid - LANG DENTAL MFG CO INC, United States).

A specific copper fixture was constructed to couple on to MTS Insight Electromechanical Testing System allowing the testing.

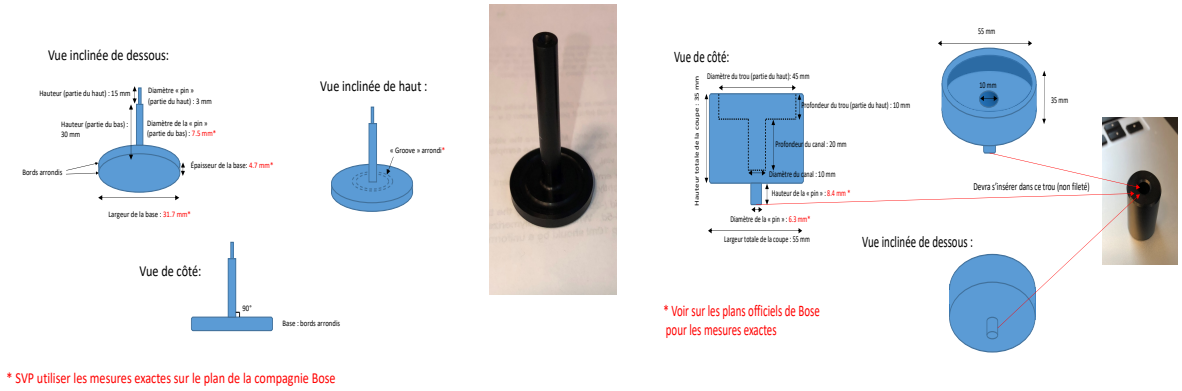

Figure 1. Design for customized push out testing pieces

The custom push out test fixture was then attached to the MTS Insight Electromechanical Testing System with a 50kN load cell and the skull pieces containing the implant, embedded in acrylic resin was placed in the customized copper piece (Figure 2).

Pushout testing was performed using a servo-hydraulic load frame (MTS Insight Electromechanical Testing System, USA) with a 50kN load cell. Once the implant was secured in the specialized fixture, load increased at a rate of 5 N/s until implant displacement occurs. The

TestWorks 4 Testing Software (MTS Systems Corporation, USA) was used to analyze the load-displacement curves and determine the load required to displace the implant, also known as “peak load”.

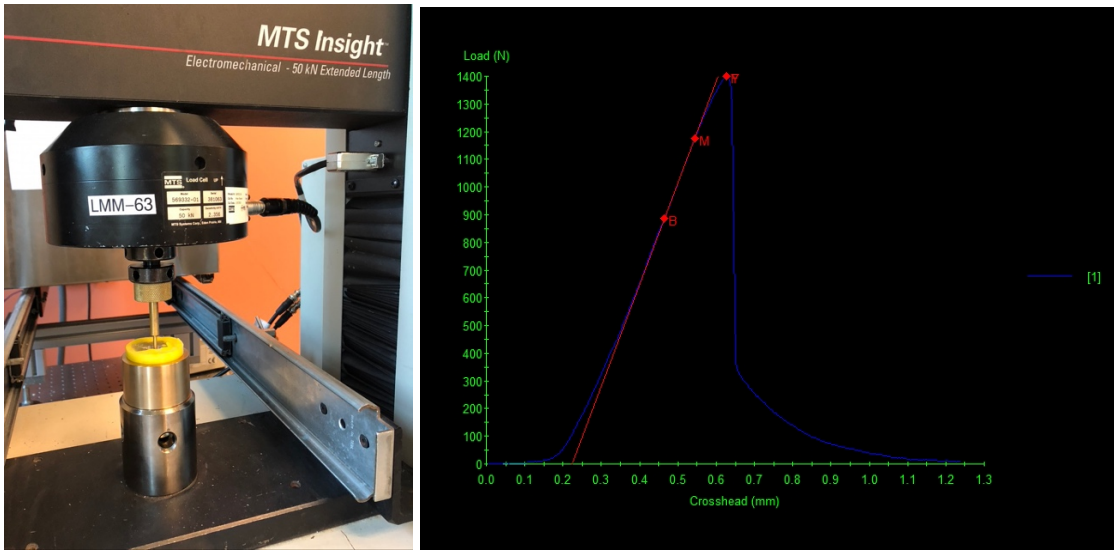

Figure 2. Image of the MTS Insight Electromechanical Testing System with a 50kN load cell. The custom pieces are in place and the skull bone piece containing the implant screw is in place. An example of the push-out load displacement curve to calculate peak load.

Micro-CT high resolution scans

Micro-CT at an isotropic voxel size of 8.0 µm (SkyScan 1276, Bruker; 70 kVp, 57 µA, no frame averaging, 0.3° rotation step, 0.5mm Al filter) was performed before and after implant placement. Cadaveric specimens from donors were cut $3cm^2$ at the temporoparietal bone region at a 40^o angle from the auditory canal (as demonstrated in Figure 12 of Chapter 1 of this thesis). The datasets were reconstructed, and 3D visualization was performed using CTAn software. Each micro-CT scan was segmented into the desired vertical volumes of interest (VOI_1) starting at the beginning of the implant screw and extending distally until its end and apposition to the implant. The second VOI looked at the microarchitecture of the skull (VOI_2). VOI_1 permitted visualization

of the bone-implant interface particularly the seating of the implant, while VOI_2 allowed for the analysis of overall skull bone outcome parameter such as overall thickness, as well as the thickness of the cortical shells, and a trabecular area (diploë).

Bone density parameters investigated include total bone mineral density (TtBMD), cortical bone mineral density (CtBMD), trabecular bone mineral density (TbBMD), and trabecular bone volume fraction (BVTV). Measured microarchitecture parameters include cortical thickness (CtTh), cortical porosity (CtPo), trabecular number per unit length (TbN), trabecular separation (TbSp), trabecular porosity (TbPo) and trabecular thickness (TbTh).

The first cortical shell (outer table) was extracted from each specimen to undergo further analysis. The obtained samples were scanned with microcomputed tomography (SkyScan 1172, Bruker, Kontich, Belgium). The following scanning parameters were used: isotropic voxel size of 2 μm, peak voltage of 100 kVp, Aluminium-Copper filter (0.5 mm Al, 0.038 mm Cu), source current of 100 μA, 0.2° rotational steps for 180°, and frame averaging of 3. The image sets were reconstructed using NRecon (Bruker, Kontich, Belgium) and InstaRecon.

Toughness Testing

For toughness testing, cadaveric samples were cut with a low-speed hand saw and then ground with silicon carbide paper to approximate cross-sectional dimensions of 2.5-mm width and 1.5-mm thickness. The fracture-toughness samples contained a notch oriented with the nominal crack-growth direction in the inferior-superior direction. Notches were cut with a low-speed diamond saw and then sharpened with a razor blade that was continually irrigated with 1-μm diamond slurry producing micronotches with a root radius of approximately 3–5 μm and an initial crack length of a ≈ 1 mm. The resulting toughness specimens were ground and polished to a 0.05-

μm finish. All samples were stored in HBSS at 25 °C for at least 12 h prior to testing (Zimmermann et al., 2010).

In accordance with American Society for Testing and Materials (ASTM) standard (https://www.astm.org/Standards/E1820), samples were loaded in three-point bending using a Gatan microtest stage (Deben, Suffolk, UK) with a span, S, equal to 8 mm and a 2kN load cell. The stage was fixed in a light microscope (DSX510, Olympus) to monitor the crack path during toughness testing. During the mechanical test, the sample was loaded at a constant displacement rate of 0.033 mm/min and the load-displacement curve was recorded. When crack growth occurred, the displacement stage was stopped and images of the extended crack were taken with the light microscope at 10x. The samples were tested until crack extension, Δa, was approximately 0.5 to 0.75 of the ligament, b, where b = W-a.

From the data, the J-R curve was constructed based on ASTM standard E1820-20 (https://www.astm.org/Standards/E1820). Here, J was calculated from the applied loads and the imaged crack extension. The non-linear strain energy release rate, J, to measure the elastic and inelastic contributions to the toughness where

$$J = J_{el} + J_{pl}$$

J_{el} is the contribution to the toughness from the elastic deformation and can be computed from the mode-I stress intensity factor, K_I, and the Young's modulus, E.

$$J_{el} = \frac{K_I^2}{E}$$

Here, the elastic modulus was assumed to be 12 GPa for human bone. The contribution to the toughness from plastic deformation, J_{pl} , is determined by the following equation:

$$J_{pl(i)} = \left[J_{pl(i-1)} + \left(\frac{1.9}{b_{i-1}}\right)\left(\frac{A_{pl(i)} - A_{pl(i-1)}}{B}\right)\right]\left[1 - 0.9\left(\frac{a_{(i)} - a_{(i-1)}}{b_{i-1}}\right)\right]$$

where A_{pl} is the area under the force-displacement curve, b is the uncracked ligament length ($b_i = W - a_i$), and B is the sample thickness. The K-based fracture toughness values, K_j, were backcalculated based on the following relationship: $K_J = (J/E)^{1/2}$.

RESULTS

Sawbone and ISQ

Preliminary analysis of the bone quality – ISQ relation was conducted in two artificial Sawbone materials replicating cortical bone and osteoporotic compromised bone. Scores obtained from Cortical bone (n = 24 measurements conducted in 4 samples) had a raw mean ISQ score of 79.71 ± 11.95, while scores obtained from osteoporotic samples (n = 24 measurements conducted in 4 samples) had a raw mean ISQ score of 46.38 ± 11.72. T-test revealed a significant difference in scores between these two cohorts (t-value = 33.55955, p-value < .00001).

Cadaveric skull donor characteristics and implant type

The temporoparietal skull bone from 29 donors (7 males, 13 females) was obtained. Table 1 summarizes the donor demographics (age of death, gender, cause of death), while table 2 tabulates the implant characteristics. All implants placed were 4mm in diameters.

Table 1a. Characteristic of cadaveric donors

Specimen #	Age	Gender	Comorbidities	Cause of death
1	67	M	COPD / mast cell activation syndrome / pulmonary fibrosis / pulmonary hypertension	respiratory failure
3	87	M	pulmonary sepsis / Alzheimer's	respiratory failure
11	46	F		cervical cancer
16	79	F	COPD	respiratory failure
31	86	M	ischemic cardiomyopathy	cardiogenic shock
32	77	F		heart failure
37	83	F		pancreatic cancer

41	68	F	non squamous cell lung cancer / malignant pleural effusion	pulmonary embolism
43	85	M	Alzheimer's	chronic renal failure
44R	82	F	pneumonia / hypertension	cardiovascular accident
44L	82	F	pneumonia / hypertension	cardiovascular accident
46R	53	F		breast cancer
46L	53	F		breast cancer
8	102	M	bacteriuria	respiratory distress / cardiac insufficiency / influenza A
24	95	F	atrial fibrillation / generalized anxiety disorder / valvulopathy	aspiration pneumonia / neurocognitive disorder type mixed
54	62	F	smoking	lung cancer stage IV / emphysema
26	88	M	CAD	metastatic prostate adenocarcinoma
10	84	F	CAD / diabetes / IRC / meurocognitive disorder / ACU	heart failure / pneumonia
2	87	F		invasive ureteral cancer
13	70	M	type 1 diabetes	heart disease / COPD / pulmonary fibrosis

ACU = acute care unit, CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, IRC = chronic renal insufficiency.

Table 1b. Summary of cadaveric donor

Characteristic	n	Mean	Median	Range
Age at death (in years)				
Identified age	20	76.8	82	46 – 102
Unknown	9			
Gender				
M	7			
F	13			
Unknown	9			
Cause of death				
Respiratory	5			
Cardiac	4			
Cancer	7			

Renal Failure	1			
Mixed	3			
Unknown	9			

Table 2. Implant characteristics

Characteristic	n
Abutment Length *	
6mm	21
9mm	8
Implant Type	
Oticon M51137	21
Oticon M51136	8

* screw diameter 4mm for all implants placed

Short term reproducibility of ISQ measurements

Two precision errors were calculated; for the first ISQ measurement (n = 60), after implant placement 3-5 days after the first measurement (n = 60). The precision errors were 6.78 ± 2.14 and 7.03 ± 2.07, respectively.

Peak load and ISQ

A regression analysis shows a relatively low R^2 (0.1285 and 0.241) for the correlation of peak load and low and high ISQ scores, respectfully. The linear regression indicates a positive relationship between peak load and mean high and low ISQ scores (Figures 3a and 3b).

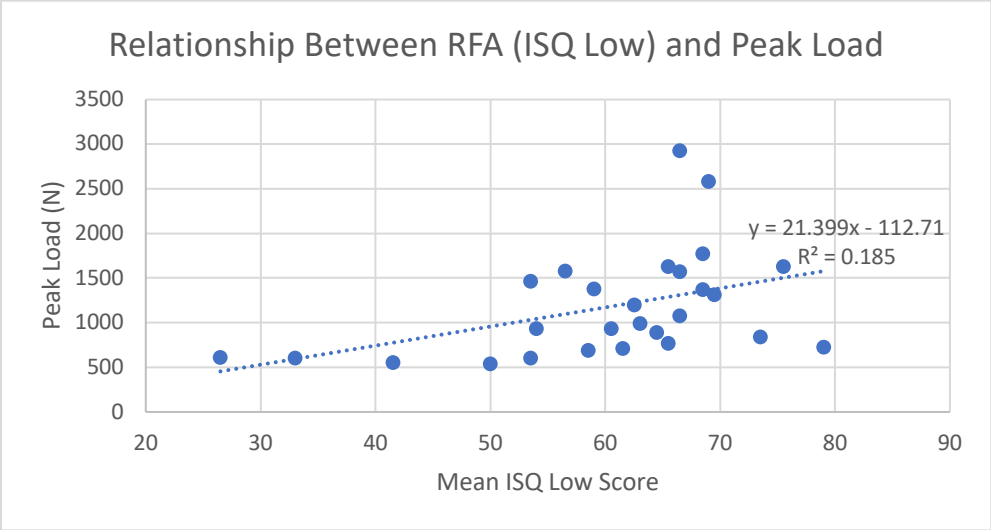

Figure 3a. Linear regression analysis demonstrating positive linear relationship between ISQ low score and peak load on a scatter plot

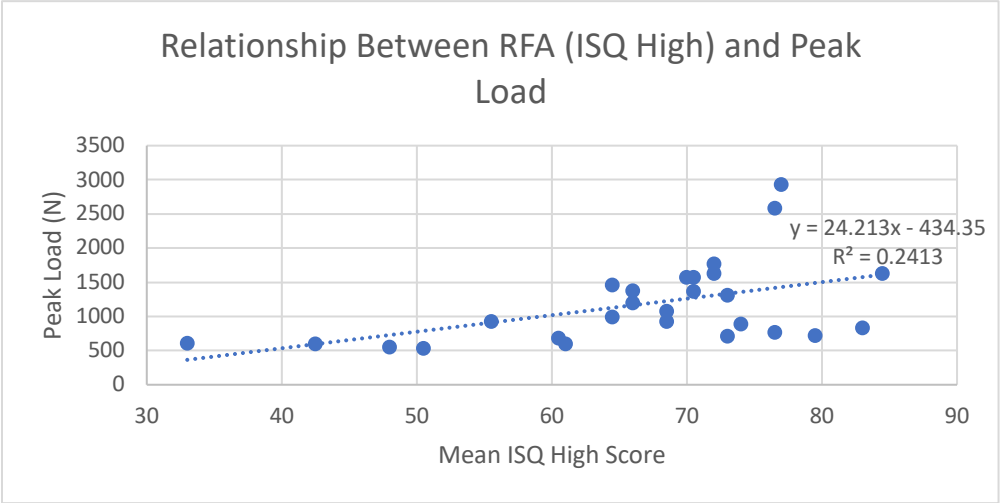

Figure 3b. Linear regression analysis demonstrating positive linear relationship between ISQ high score and peak load on a scatter plot

Age of donor, gender, and peak load

A linear regression analysis shows a positive correlation between peak load and age of the donor. An outlier was identified altering the R^2 (0.160).

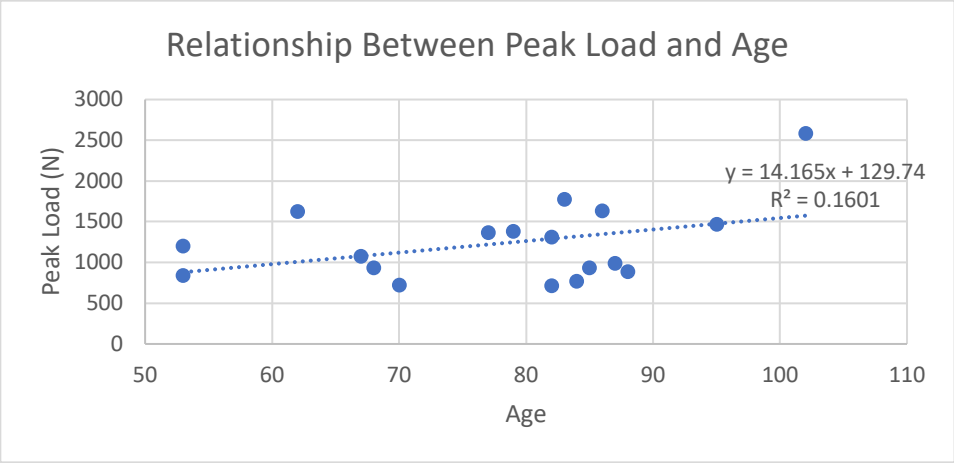

Figure 4a. Linear regression analysis demonstrating positive linear relationship between peak load and age of donor on a scatter plot.

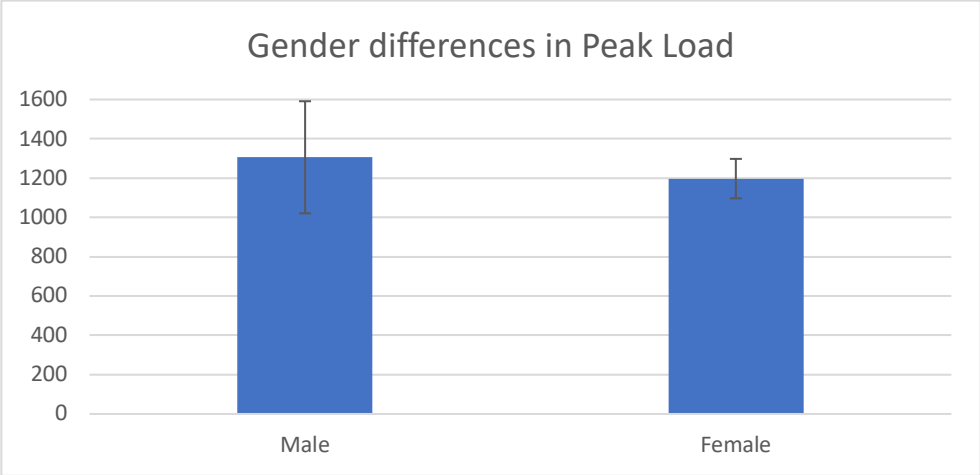

Figure 4b. Gender differences in peak load (t-test = 0.414, df = 14)

Age of donor and ISQ measurement

A regression analysis shows relatively no correlation between the age of the donor and the stability scores measured; R^2 (0.075and 0.018).

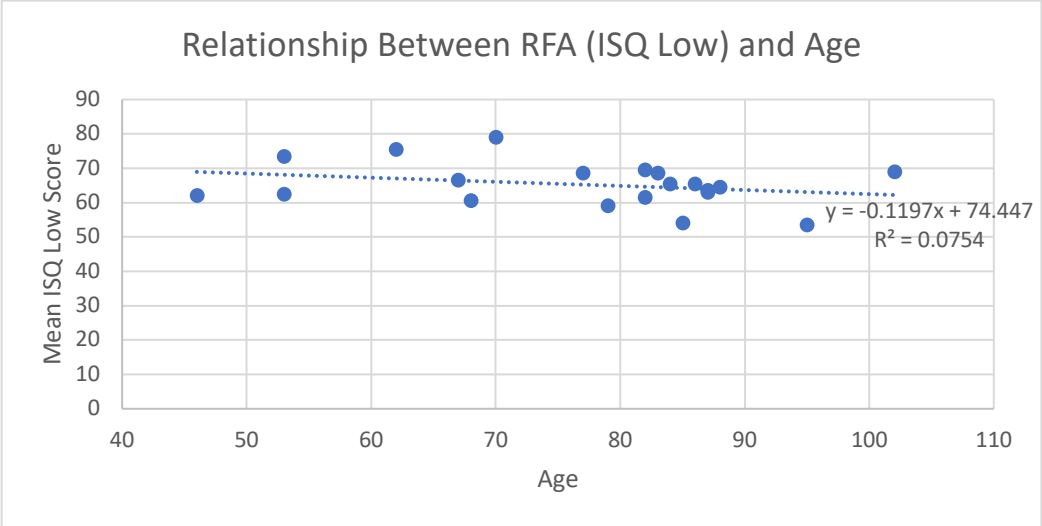

Figure 5a. Linear regression analysis demonstrating non-linear relationship between ISQ low score and age of donor on a scatter plot.

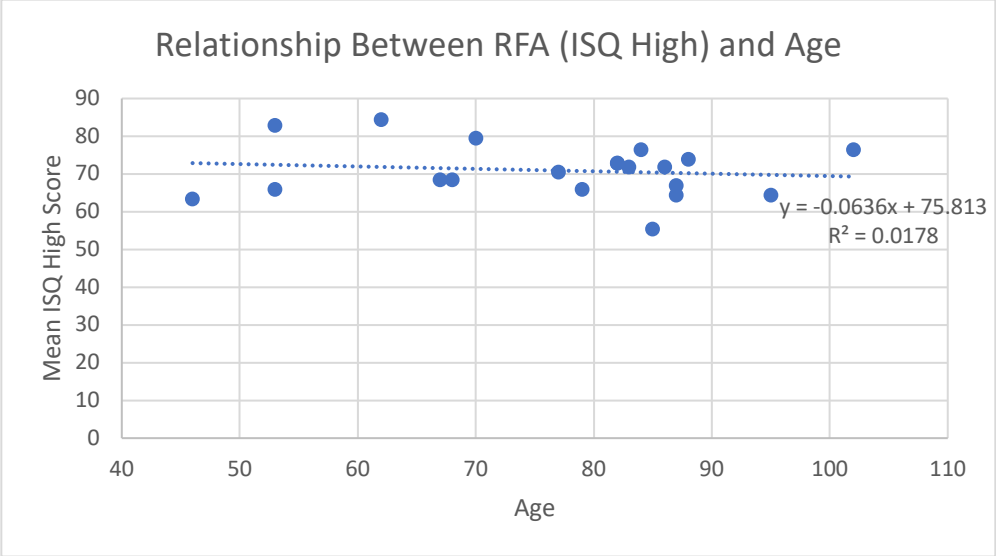

Figure 5b. Linear regression analysis demonstrating non-linear relationship between ISQ High score and age of donor on a scatter plot.

Table 3. Average peak values and ISQ scores per age cohort

AGE OF COHORT	AVERAGE PEAK VALUE	AVERAGE ISQ SCORE
45-60	1019.50	68.42

61-75	1090.37	72.81
76-90	1175.99	66.68
91-	2024.02	65.88

Fracture toughness test

A regression analysis shows a correlation R^2 (0.206 and 0.468) when investigating the relationship between the age of the donor and crack initiation and crack growth. The linear regression indicates a negative relationship between age of donor and crack initiation (Figure 6a), and a positive relationship between age of donor and crack growth (Figure 6b). In materials science, fracture toughness is the critical stress intensity factor of a sharp crack where propagation of the crack suddenly becomes rapid and unlimited (shown in Figure 7).

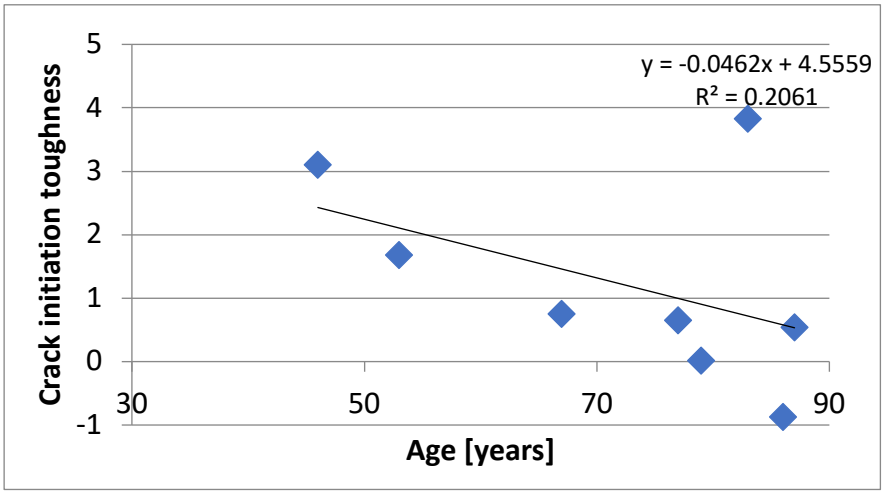

Figure 6a. Linear regression analysis demonstrating linear relationship between the age of the donor and crack initiation toughness on a scatter plot.

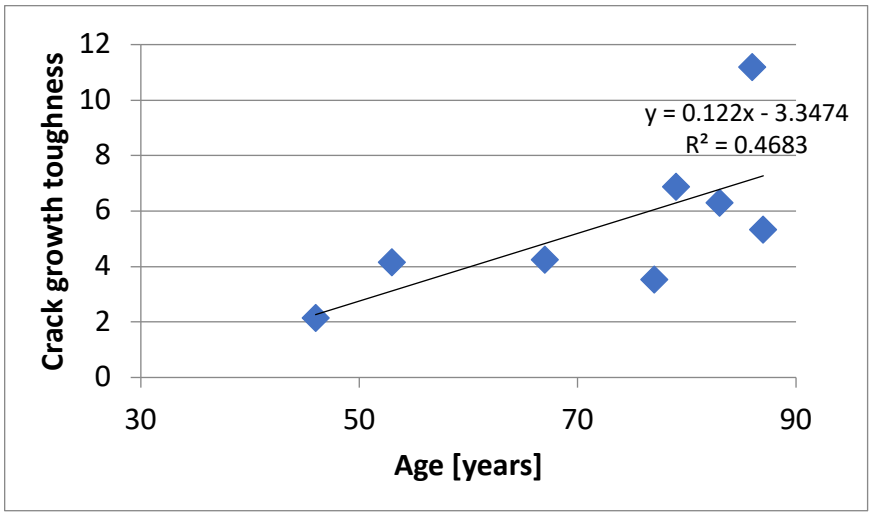

Figure 6b. Linear regression analysis demonstrating linear relationship between the age of the donor and crack growth toughness on a scatter plot.

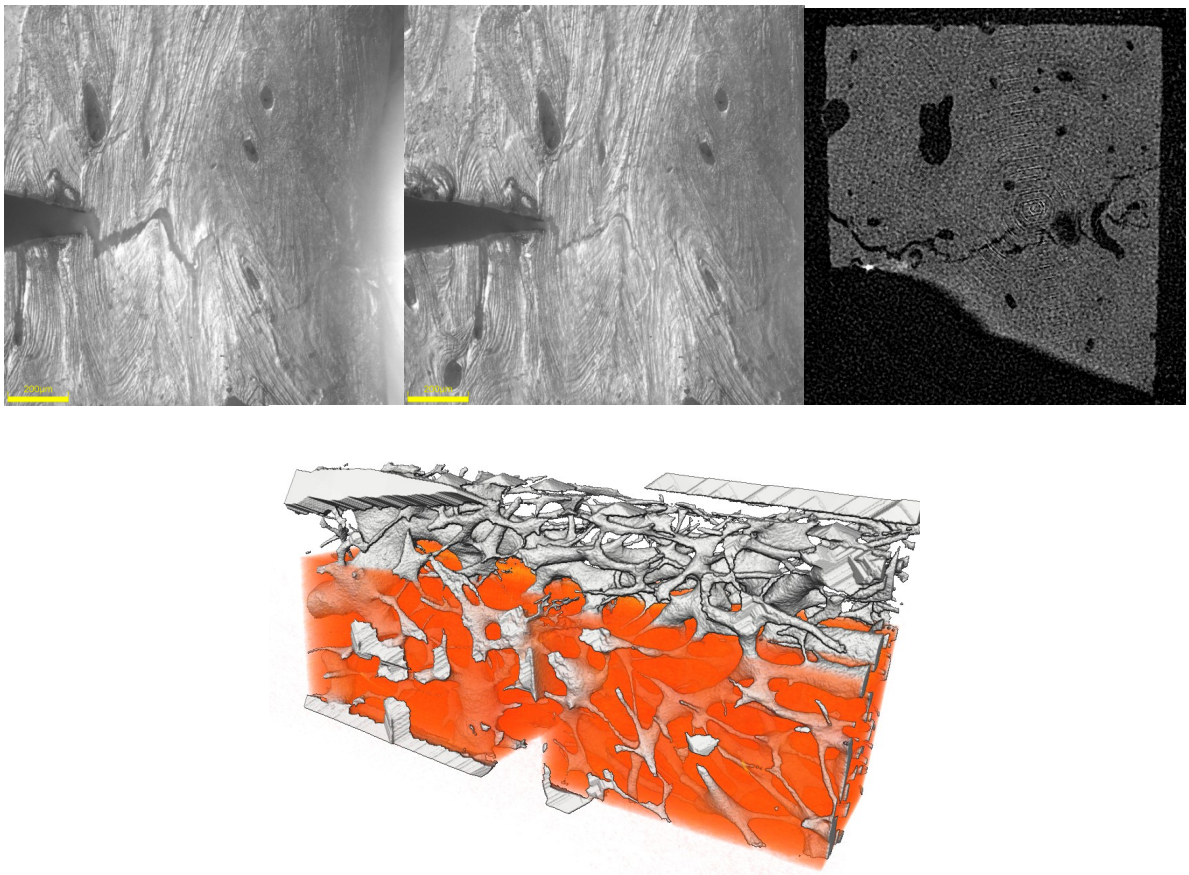

Figure 7. Micro-CT images of the fracture toughness testing procedure showing the trajectory of the crack growth from the point of initiation.

Micro CT imaging

To investigate the integrity and features of the host bone receiving the implant, we opted for the bone 2mm next to the site the implant was placed. This allowed us to have a better understanding and predict the integrity of the host bone. (Figure 8)

Bone density parameters and measured microarchitecture parameters described in the methodology will be further investigated. These measurements and subsequent analysis are still ongoing.

Qualitative assessment showed bone in apposition with the implant seated (Figure 8). In three specimens, we were able to visualize the screw penetrating the inner cortical shell, suggesting insufficient skull thickness for implantation.

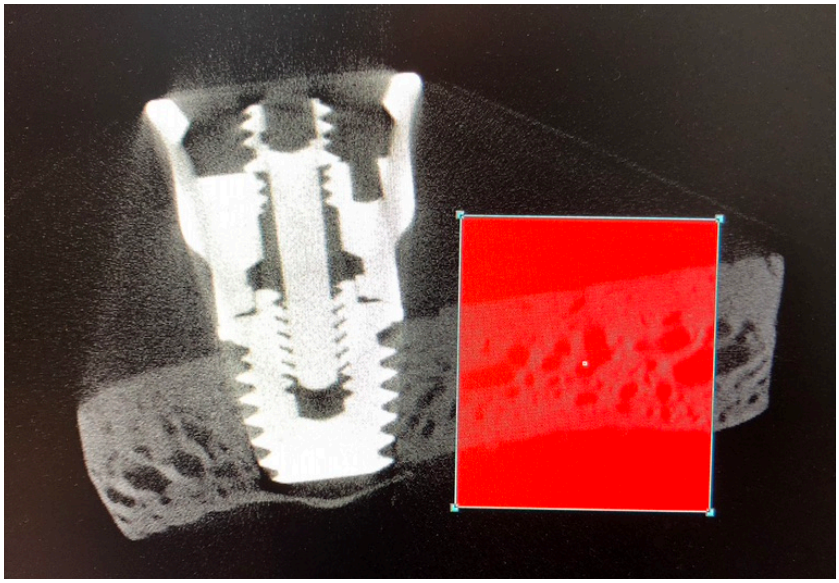

Figure 8. Area of interest in red investigated for the host site for the bone anchored hearing implant screw (VOI_2)

DISCUSSION

Osseointegration of titanium implants is a widely applied phenomenon, originating in orthopedic research by Brånemark et al. since 1952 (Brånemark et al., 1983). Titanium implants were first intraorally in the field of dentistry. Since 1977, roughly the same implant design is used percutaneously in the temporal bone, permitting firm attachment of a sound processor for bone conduction hearing (Tjellström et al., 1981). Researcher in the field of osseointegrated implant have longed searched for a non-invasive and objective way to measure the integrity of the bone-implant interface. Resonance frequency analysis (RFA) was introduced by Meredith et al. to clinically test implant stability in a non-destructive manner (Meredith et al., 1998). The RFA technique is essentially a bending test of the bone-implant system in which an extremely small

bending force is applied by stimulating a transducer. RFA has been widely applied in research on dental implants, but little is known in terms of what the RFA measures particularly for auditory implants fixated in the temporoparietal skull bone region. RFA in clinical research on auditory osseointegrated implants is a novel technique.

This cadaveric study is the first to demonstrate positive correlations between ISQ values and peak load for auditory implants placed in skull bone. This indicates that the higher the ISQ score, the more Newton force is required to displace the bone anchored implant. Thus, ISQ seems to accurately predict the fixation strength of the bone-implant interface. It was also demonstrated that crack growth toughness increases with age, while crack initiation toughness decreases with age similarly to the literature investigating the effect of aging on the toughness of human cortical bone (Koester et al., 2011; Nalla et al., 2004).

It is known that bone anchored hearing implant loss is most common in children (Bezdjian et al., 2018). This is greatly attributed to the active lifestyles and play activities that children are subjected to making them inherently at higher risk for traumatic implant losses. Age-dependent structural bone differences may also be related to BAHI losses. Younger bone anchored hearing implant recipients can present with softer, thinner, and immature skull bone containing air cells generally filled with bone marrow cells and an extensive blood supply (Drinias et al., 2007). Post-operatively, softer, more compliant bone may not tolerate the BAHI processor load, leading to excessive micromotion during the important initial healing phase (Willie et al., 2010; Pilliar et al., 1986). Thus, this could necessitate a longer osseointegration period and require delayed processor coupling protocols.

As the aging process occurs, bone resorption often exceeds bone formation, thereby reducing bone mass and increasing fragility. There is an accompanying age-related reduction in

the bone formation response to mechanical loading that likely deleteriously affects healing around the implants (Chan et al., 2002; Razi et al., 2015; Srunivasan et al., 2012). Furthermore, previous retrospective studies have suggested that longer-term implant losses are more likely to be associated with patient-related factors (Bezdjian et al., 2018; den Besten et al., 2015). These factors include previous radiotherapy exposure to the temporoparietal skull, diabetes, cardiovascular disease, smoking, alcohol abuse, and various medication uses. There is evidence to suggest that the aforementioned factors have a biochemical and clinical effect on bone metabolism, bone perfusion, and ultimately on osseointegration. Other comorbidities that have been present in patients with BAHI include mental retardation, Treacher-Collins syndrome, Pierre-Robbin syndrome, Cornelia de Lang syndrome, and Morbus Addison disease (Bezdjian et al., 2018).

The non-linear relationship between temporal skull bone thickness, a crucial factor in osseointegration and implant stability, and age has been well-established (Baker, 2016; Lillie, 2015; Lynnerup, 2005; Tomlinson, 2017). Accordingly, while the non-linear relationship between ISQ scores and age of donor was expected, the positive correlation between peak load and age of donor was a noteworthy finding for two reasons. First, cadaveric bone is not living bone, meaning that age-related dynamic bone-processes should not have an impact on BAHI stability post-implantation. Second, age-related skull bone properties have not been previously shown to offset the aforementioned non-linear relationship between temporal skull bone thickness and age. This is a key finding due to the current paucity in knowledge regarding the effect of age as a factor in auditory implant stability.

Similarly, an investigation into the role of gender as a factor in bone quality and implant stability is warranted. Previous studies demonstrate a non-linear relationship between gender and temporal skull bone thickness as well as a non-significant effect of gender on age-related temporal

skull thickness changes (Lillie, 2015; Lynnerup, 2005). In the field of dental implants, previous studies have demonstrated a significant effect of gender on implant stability in the short-term (Andersson, 2019; Guler, 2013). In particular, dental implants have been shown to yield significantly higher ISQ scores in men directly after implantation and up to 4 weeks after implant placement. However, gender did not have an effect on long-term implant stability or survival in any of these studies. It is also worth mentioning that these studies had relatively long wait periods between follow-up measurements, meaning that it is difficult to make definitive conclusions about dental implant stability trends over time. Ultimately, it remains to be seen how the effect of gender on dental implants would translate into the field of BAHI stability in the temporal skull bone.

It is still rudimentary to determine the added value of RFA in clinical practice. The precision analysis in this study shows a lack of reproducibility that make incidental ISQ values alone limited in determining objectively the integrity of the implant anchorage (Nelissen et al., 2015). Nonetheless, changes in individual ISQ threshold shifts within the same implant at follow-up visits could indicate implant stability failure. Due to its non-invasive nature, it is encouraged to use RFA in clinical practice and perform longitudinal observations of ISQ trends. When implant failure is encountered, delaying or halting the processor coupling is recommended.

Limitations of this study include the age of cadavers donated. It would be interesting to replicate the outcomes of this study in younger skull bones. Moreover, the cadaveric specimens were embalmed with formaldehyde influencing its biological properties. This could alter the replicability between the skull bone used in the study and in-vivo skull. Clinical studies have demonstrated that cortical thickness is strongly correlated to an increase in primary stability as measured by the ISQ score (Merheb et al., 2017). Investigation of the relation between ISQ scores and thickness of the temporoparietal skull bone is warranted.

CONCLUSION

The RFA system accurately predicts the force required to displace the implant. Skull bone characteristics in cadavers did not influence the stability outcomes measured. Age-related skull bone properties might have an effect on the RFA measurement. The added value of the RFA system needs to be further investigated in younger bone samples and in in-vivo models to assess its relation with osseointegration.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Dr. Geoffroy Noel and Mr. Jamie Brisebois from the Division of Anatomical Sciences at McGill University for collecting the specimens. This research was made possible by the generosity of the donors and their families. The authors would like to thank Dr. Martin Johansson and Oticon Medical for providing the implants used in this research. This study was funded by the Shriners Hospitals for Children, FRQS Programme de bourses de chercheur (B.W. and M.R.), and NSERC – Alexandre Graham Bell training scholarship (A.B.).

REFERENCES

Andersson P, Pagliani L, Verrocchi D, et al. Factors Influencing Resonance Frequency Analysis (RFA) Measurements and 5-Year Survival of Neoss Dental Implants. Int J Dent 2019;2019:3209872. doi: 10.1155/2019/3209872

Apostu D, Lucaciu O, Berce C, et al. Current methods of preventing aseptic loosening and improving osseointe- gration of titanium implants in cementless total hip arthroplasty: A review. J Int Med Res 2018;46:2104–19.

Baker AR, Fanelli DG, Kanekar S, Isildak H. A retrospective review of temporal bone imaging with respect to bone-anchored hearing aid placement. Otol Neurotol 2017;38(1):86–88.

Baker A, Fanelli D, Kanekar S, Isildak H. A review of temporal bone CT imaging with respect to pediatric bone-anchored hearing aid placement. Otol Neurotol 2016;37(9):1366–1369.

Bezdjian A, Smith RA, Thomeer HG, et al. A systematic review on factors associated with percutaneous bone anchored hearing implants loss. Otol Neurotol 2018;39(10):e897-e906. doi: 10.1097/MAO.0000000000002041

Bezdjian A, Smith RA, Gabra N, et al. Experience with minimally invasive ponto surgery and linear incision approach for pediatric and adult bone anchored hearing implants. Ann Otol Rhinol 2019;129(4):380–387.

Brånemark PI. Osseointegration and its experimental background. J Prosthet Dent 1983;50:399–410.

Calon TGA, Johansson ML, de Bruin AJG, et al. Minimally invasive ponto surgery versus the linear incision technique with soft tissue preservation for bone conduction hearing implants: A multicenter randomized controlled trial. Otol Neurotol. 2018;39(7):882-893.

Chan GK, Duque G. Age-related bone loss: Old bone, new facts. Gerontology 2002;48:62–71.

Demontiero O, Vidal C, Duque G. Aging and bone loss: New insights for the clinician. Ther Adv Musculoskelet Dis 2012;4: 61–76.

den Besten CA, Nelissen RC, Peer PG, et al. A retrospective cohort study on the influence of comorbidity on soft tissue reactions, revision surgery, and implant loss in bone-anchored hearing implants. Otol Neurotol 2015;36(5):812–818.

Drinias V, Granström G, Tjellström A. High age at the time of implant installation is correlated with increased loss of osseointegrated implants in the temporal bone. Clin Implant Den Relat Res 2007;9:94 – 9.

Dun CA, Faber HT, de Wolf MJ, Mylanus EA, Cremers CW, Hol MK. Assessment of more than 1,000 implanted percutaneous bone conduction devices: skin reactions and implant survival. Otol Neurotol 2012;33(2):192-198.

Falland-Cheung L, Waddel JN, et al. Investigation of the elastic modulus, tensile and flexural strength of five skull simulant materials for impact testing of a forensic skin/skull/brain model. J Mec Behav Biomed Mat 2017;68:303-7.

Glüer CC, Blake G, Lu Y, et al. Accurate assessment of precision errors: how to measure the reproducibility of bone densitometry techniques. Osteoporos Int 1995;5(4):262-70. doi: 10.1007/BF01774016. PMID: 7492865.

Goldhahn J, Suhm N, Goldhahn S, et al. Influence of osteoporosis on fracture fixation—a systematic literature review. Osteoporos Int 2008;19:761–72.

Guler AU, Sumer M, Duran I, Sandikci EO, Telcioglu NT. Resonance frequency analysis of 208 Straumann dental implants during the healing period. J Oral Implantol 2013;39(2):161-167. doi: 10.1563/AAID-JOI-D-11-00060

Hogsbro M, Agger A, Johansen LV. Successful loading of a bone-anchored hearing implant at 1 week after surgery. Otol Neurotol 2017;38(2):207-211.

Hultcrantz M, Lanis A. A five-year follow-up on the osseointegration of bone-anchored hearing device implantation without tissue reduction. Otol Neurotol 2014;35(8):1480-5.

Isaacson BM, Vance RE, Chou TG, et al. Effectiveness of resonance frequency in predicting orthopedic implant strength and stability in an in vitro osseointegration model. J Rehabil Res Dev 2009;46(9):1109-1120.

Johansson ML, Stokroos RJ, Banga R, et al. Short-term results from seventy-six patients receiving a bone-anchored hearing implant installed with a novel minimally invasive surgery technique. Clin Otolaryngol. 2017;42(5):1043-8.

Kim WY, Han CH, Park JI, Kim JY. Failure of intertrochanteric fracture fixation with a dynamic hip screw in relation to pre-operative fracture stability and osteoporosis. Int Orthop 2001;25:360–2.

Koester KJ, Barth HD, Ritchie RO. Effect of aging on the transverse toughness of human cortical bone: evaluation by R-curves. J Mech Behav Biomed Mater. 2011;4(7):1504–13. doi: 10.1016/j.jmbbm.2011.05.020

Kruyt IJ, Banga R, Banerjee A, et al. Clinical evaluation of a new laser-ablated titanium implant for bone-anchored hearing in 34 patients: 1-year experience. Clin Otolaryngol 2018;43(2):761–764.

Lillie EM, Urban JE, Lynch SK, et al. Evaluation of skull cortical thickness changes with age and sex from computed tomography scans. J Bone Miner Res 2016;31(2):299-307. doi: 10.1002/jbmr.2613

Lynnerup N, Astrup JG, Sejrsen B. Thickness of the human cranial diploe in relation to age, sex and general body build. Head Face Med 2005;1:13.

Meredith N. Assessment of implant stability as a prognostic determinant. Int J Prosthodont. 1998;11:491–501.

Merheb, J, Vercruyssen, M, Coucke, W, Quirynen, M. Relationship of implant stability and bone density derived from computerized tomography images. Clin Implant Dent Relat Res 2018;20:50–57. doi: 10.1111/cid.12579

Nalla RK, Kruzic JJ, Kinney JH, Ritchie RO. Effect of aging on the toughness of human cortical bone: evaluation by R-curves. Bone. 2004 Dec;35(6):1240-6. doi: 10.1016/j.bone.2004.07.016. PMID: 15589205.

Nazari A, Bajaj D, Zhan D, et al. Aging and the reduction in fracture toughness of human dentin. J Mech Behav Biomed Mater. 2009 Oct;2(5):550-9.

Nelissen RC, Wigren S, Flynn MC, et al. Application and interpretation of resonance frequency analysis in auditory osseointegrated implants: A review of literature and establishment of practical recommendations. Otol Neurotol. 2015;36:1518-1524.

Pilliar RM, Lee JM, Maniatopoulos C. Observations on the effect of movement on bone ingrowth into poroussurfaced implants. Clin Orthop Relat Res 1986;208:108–13.

Razi H, Birkhold AI, Weinkamer R, et al. Aging leads to a dysregulation in mechanically driven bone forma- tion and resorption. J Bone Miner Res 2015;30:1864–73.

Sayardoust S, Omar O, Thomsen P. Gene expression in peri-implant crevicular fluid of smokers and nonsmokers. 1. The early phase of osseointegration. Clin Implant Dent Relat Res. 2017;19(4):681-693.

Shah FA, Johansson ML, Omar O, et al. Laser-modified surface enhances osseointegration and biomechanical anchorage of commercially pure titanium implants for bone-anchored hearing systems. PLoS ONE 2016;11(6):e0157504.

Snik AFM, Mylanus EAM, Proops DW, et al. Consensus statements on the BAHA system: where do we stand at present? Ann Otol Rhinol Laryngol 2005;114(195):1–12.

Soballe K, Hansen ES, Rasmussen H, Jorgensen PH, Bunger C. Tissue ingrowth into titaniumand hydroxyapatitecoated implants during stable and unstable mechanical conditions. J Orthop Res 1992;10:285.

Srunivasan S, Gross TS, Bain SD. Bone mechanotransduction may require augmentation in order to strengthen the senescent skeleton. Ageing Res Rev 2012;11:353–60.

Tjellström A, Granström G. One-stage procedure to establish osseointegration: a zero to five years follow-up report. J Laryngol Otol 1995;109:593–598.

Tjellström A, Lindström J, Hallén O, Albrektsson T, Braånemark PI. Osseointegrated titanium implants in the temporal bone. A clinical study on bone-anchored hearing aids. Am J Otol 1981;2:304–10.

Tomlinson AR, Hudson ML, Horn KL, et al. Pediatric calvarial bone thickness in patients with and without aural atresia. Otol Neurotol 2017;38(10):1470–1475.

Verheij E, Bezdjian A, Grolman W, Thomeer HG. A systematic review on complications of tissue preservation surgical techniques in percutaneous bone conduction hearing devices. Otol Neurotol 2016;37(7):829-37.

Willie BM, Yang X, Kelly NH, et al. Cancellous bone osseointegration is enhanced by in vivo loading. Tissue Eng Part C Methods 2010;16:1399–406.

Wood, MR, Vermilyea SG. A review of selected dental literature on evidence-based treatment planning for dental implants: report of the Committee on Research in Fixed Prosthodontics of the Academy of Fixed Prosthodontics. J Prosthet Dent 2004; 92:447–462

Zimmermann EA, Launey ME, Ritchie RO. The significance of crack-resistance curves to the mixed-mode fracture toughness of human cortical bone. Biomaterials 2010;31(20):5297–305. doi: 10.1016/j.biomaterials.2010.03.056

LINKING STATEMENT

Challenges in bone anchored hearing implant research rely in the fact that in-vivo clinical investigations are limited to subjective outcomes seen peri-operatively. Studies of the sort help the auditory implant research community to translate animal and ex-vivo cadaver studies to clinical scenarios. Challenges in this rely in the size of the implant and the composition of the skull that prevents researchers from using small animals. Cadaveric research, although resembling in size and composition, does not permit translation of in-vivo bodily responses occurring at the site of the implant.

In certain cases, like the next study, a case report alongside research in other fields such as dentistry can help the auditory implant community better understand underlying factors behind bone anchored hearing implant stability impedance.

3.4 Smoking affects stability

Smoking as a risk factor for spontaneous bone anchored hearing implant extrusion

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Published in: Otolaryngology Case Reports, Volume 14, March 2020, 100140

ABSTRACT

Purpose: Numerous studies have identified smoking as a risk factor for osteoporosis and bone fracture. Higher revision rates of orthopedic hip and knee replacements as well as dental implants in smokers compared to nonsmokers are known. There are limited reports examining the effect of smoking on bone anchored hearing implant survival (BAHI).

Methods and Materials: We report a case of two BAHI extrusions occurring in a heavy smoker patient. The literature was reviewed to investigate the association between BAHI loss and smoking and the possible underlying mechanisms that may account for auditory osseointegrated implant loss and smoking.

Results: The patient experienced delayed healing and increased pain around the abutment site. After the first extrusion, a revision surgery was conducted. Both surgeries were unproblematic. After sound processor coupling, the implanted extruded after 2 days and again 1 week after a revision surgery. The timing of the implant loss suggests that the bone implant interface did not achieve adequate primary stability through the surgeries and osseointegration never occurred.

Conclusion: Contributors to bone strength such as bone mineral density and microstructure are deleteriously affected by smoking. Smoking has been associated with significantly increased risk for fracture. Smoking may lower bone mass via direct effects on bone cells or indirectly affecting calcium absorption and vitamin D metabolism, adrenal and gonadal hormone levels, and/or free radical levels. Smoking adversely affects hormones and enzymes involved in bone regulation, and has inhibitory effects on osteogenesis and on angiogenesis. At the cellular level, nicotine reduces the proliferation of red blood cells, macrophages, and fibroblasts and increases micro clot formation in blood vessels through increased platelet adhesiveness. This case report and review of

literature serve to demonstrate the risks associated with bone anchored hearing implant loss and smoking. Consideration should be given when implanting BAHIs in heavy smokers.

INTRODUCTION

The bone-anchored hearing implant (BAHI) was developed in the late 70s and since then has been used successfully to rehabilitate patients with conductive or mixed hearing loss who cannot benefit from traditional hearing aids (Lustig et al., 2001). BAHIs utilize the transmission of sound through bone conduction. The device is comprised of an external sound processor coupled to an osseointegrated titanium implant screw that is inserted into the temporoparietal skull bone behind the ear. The long-term fixation of the BAHI is greatly dependent on the implant achieving good primary stability at the time of initial surgery and subsequent osseointegration, the structural and functional connection between living bone and the surface of a load-bearing implant (Parithimarkalaignan & Padmanabhan, 2013). Successful osseointegration involves a series of events including initial inflammation, bone formation, and bone remodeling (Sayardoust, Omar, Norderyd, & Thomsen, 2018).

Although not common, failure to achieve osseointegration or sudden loss of acquired osseointegration has been reported (Larsson, Tjellstrom, & Stalfors, 2015; Tjellstrom, Granstrom, & Odersjo, 2007). Early implant losses are frequently associated with a lack of initial fixation while late losses are more frequently associated with patient-related factors such as irregular bone surface or poor bone quality (Esposito, Hirsch, Lekholm, & Thomsen, 1998). Several risk factors such as peri-implant bone quality, bone density, diabetes, age, radiation exposure, and osteoporosis may jeopardize the stability outcome of osseointegrated implants (Ghanem et al., 2017). Numerous studies have identified smoking as a risk factor for osteoporosis and bone fracture (Biskobing, 2002; Kanis et al., 2005; Sayardoust et al., 2018). Several studies have reported higher revision rates of orthopedic hip and knee replacements (Parithimarkalaignan & Padmanabhan, 2013; Singh et al., 2015) as well as dental implants in smokers compared to nonsmokers (Bain & Moy, 1993;

Kasat & Ladda, 2012). Additionally, this population displays increased bone loss and increased fracture incidence compared to nonsmokers (Hollinger, Schmitt, Hwang, Soleymani, & Buck, 1999; Kanis et al., 2005).

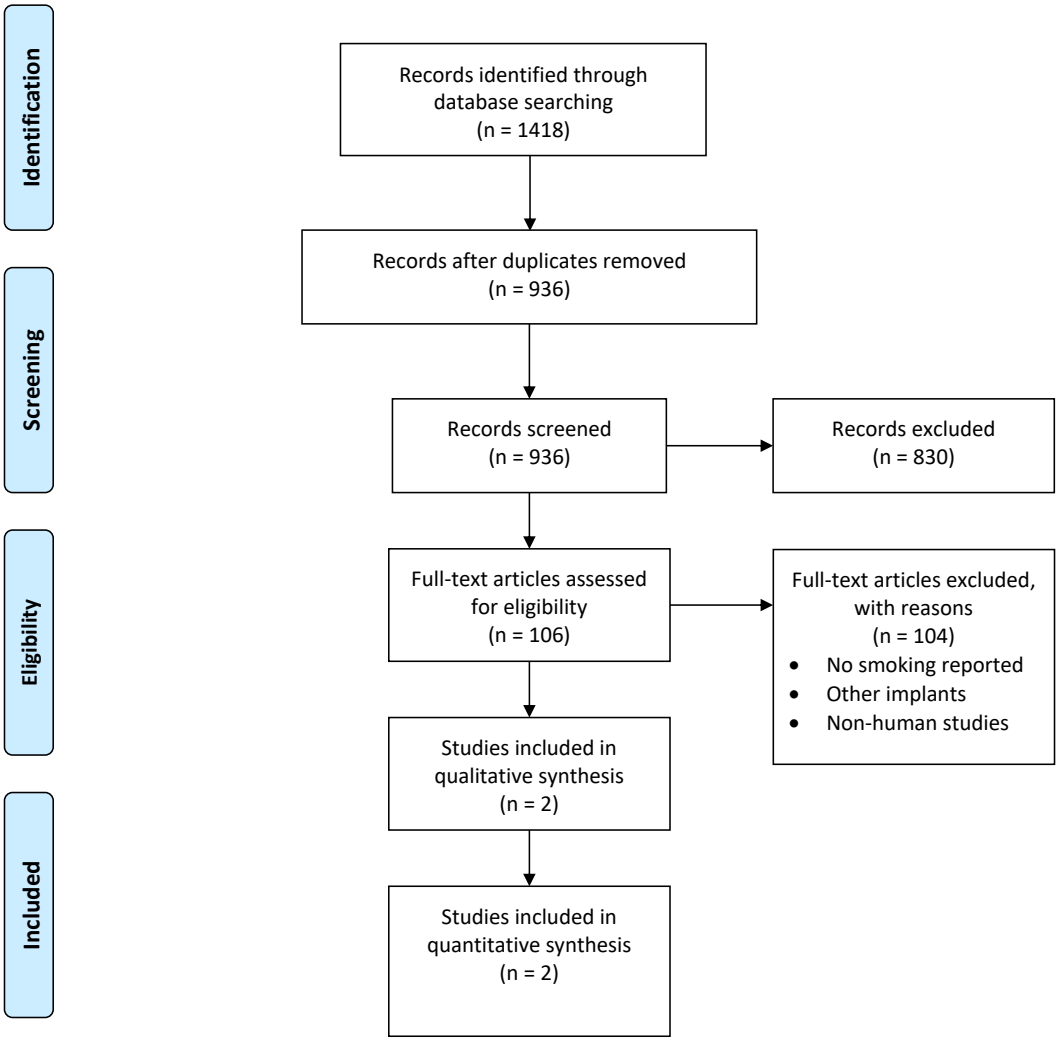
Here, we report a case of bone anchored hearing implant losses in a 35-year-old patient, who smoked 20 cigarettes/day for the last 20 years. In addition, a literature review was performed to investigate the association between implant loss and smoking. We also highlight underlying mechanisms that may account for BAHI loss in smokers.

METHODS

A literature review was conducted to identify BAHI losses in patients who are smokers. Eligible articles published between 1946 and January 30th 2019 were identified through a comprehensive search in Medline, Embase and BIOSIS electronic databases conducted by a medical librarian. Search terms included: hear or hearing or ear or ears or deaf* or auditor* or audiolog* or auricul* or cochlea* or ossic* or tympan* or vestib* or otol* or otorhin* or otorrin* or neurootol*) (aid* or device* or implant* or prosthes*) Lost or loss or lose or fail* or extrude* or extrusion or surviv* or stabili*) (implant or prosthesis or osseointegrat*). Although all types of implant losses were investigated only BAHI losses linked with smoking were retrieved for data extraction.

Retrieved articles were read in full-text by 2 authors (A.B., Z.V.). Articles presenting adult patients with a BAHI loss and who are smokers were selected. Reference list of selected articles were inspected for cross-reference examination to identify additional relevant literature. No restrictions in publication year or language were applied. Figure 1 summarizes the study selection process.

Figure 1. Flow chart demonstrating study selection process



CASE REPORT

We report a case of two bone anchored hearing implant extrusions in a 35-year-old male patient, who smoked 20 cigarettes/day for the last 20 years. Generally, someone who smokes a pack (containing 20 cigarettes) a day or more is characterized as a heavy smoker. Patient history revealed recurrent cholesteatomatous otitis media for which bilateral surgical interventions were necessary. This resulted in dry, cleaned radical cavities on both ears. There was mixed hearing loss

identified in the right ear and a maximum conductive loss in the left ear. This rendered the patient an ideal candidate for a left ear BAHI. A left ear BAHI (Oticon Ponto®, screw size 4mm; abutment length 9mm) was positioned under general anaesthesia. After position marking (45 degrees from the Frankfurter line and around 60mm from the bony ear canal), local anaesthesia (lidocaine with epinephrine) was applied followed by a punch incision enlarged by three longitudinal 0.5cm cuts (star-shaped incision). Bony cortex was visualized and freed from periosteum. With the guide drill and counter sink, a 4mm implant screw with 9mm abutment was positioned with 50Nm torque restriction. The procedure was done without any complication.

Post-operative healing was significantly delayed, and the patient experienced increasing pain around the abutment side, which necessitated local and systemic antibiotic treatment. When the infection around the wound was healed, the sound processor was coupled. Two days after coupling, the abutment screw extruded, and the implant was lost. A revision surgery was conducted similarly to the initial procedure, but more superiorly positioned than the previous implant. Similar post-operative healing problems occurred and although general and local antibiotic regimens were applied, one week after coupling, the implant extruded. No further surgeries were done.

LITERATURE REVIEW

Tjellstrom et al. investigated the survival rate of BAHIs in a case series (Tjellstrom et al., 2007). Of the 138 implants placed in the study, two were lost. One lost implant occurred in a 78-year-old man who was a heavy smoker and diabetic. Six weeks after the 4mm long self-tapping implant was inserted, the BAHI was fitted. Three months later the implant was lost.

An additional implant loss in a heavy smoker was reported by Larson et al. (Larsson et al., 2015). Of the 763 installed BAHIs, 109 implants failed due to loss of osseointegration. One patient, a heavy smoker for many years and on oral steroid mediation due to lung diseases, reported having

six implants. He lost the first three due to direct trauma and the last two implants due to loss of osseointegration. The timing of extrusion was not reported.

DISCUSSION

The success of BAHIs heavily rely on the integration of the implant surface in the host bone. Clinically, an implant is considered osseointegrated when there is no progressive relative movement between the contacted bone and implant (Mavrogenis, Dimitriou, Parvizi, & Babis, 2009). The mechanisms behind loss of osseointegration is still not fully understood. The process is complex and can be influenced by many factors that influence the formation and maintenance of bone at the implant surface (Parithimarkalaignan & Padmanabhan, 2013). Implant failures can be divided into two categories: early and late failures. Early failures describe an implants failure to establish osseointegration while late failures occur when implants fail to maintain the established osseointegration (Esposito et al., 1998).

Successful osseointegration involves a series of events including initial inflammation, bone formation, and bone remodeling (Sayardoust et al., 2018). Bone healing around implants involves a cascade of cellular events. A rich blood supply near the implant surface is important to support bone healing processes which allows for the biological fixation of the implant. The first biological components coming into contact with the implant surface are blood cells that activate and release cytokines and other soluble, growth, and differentiation factors to influence clot formation (Mavrogenis et al., 2009). The formed fibrin matrix acts as a scaffold for the migration and differentiation of osteogenic cells to induce bone healing. A thin layer of calcified and osteoid tissue is deposited by osteoblasts directly on the surface of the implant (Mavrogenis et al., 2009). This newly calcified matrix and the presence of osteogenic cells induce the formation of new woven and trabecular bone. The part of the skull where the BAHI is implanted is the squamous

portion of the temporal bone, which is made up of a cortical bone shell that encases trabecular bone.

Bone remodeling occurs at the bone-implant interface as adaptations to mechanical stimuli. Implant loading ultimately leads to micromotions at the bone-implant interface. It is well-established that micromotion during initial phases of bone healing can compromise implant osseointegration (Parithimarkalaignan & Padmanabhan, 2013). The temporal bones of the skull are only minimally loaded by muscle actions and thus normally undergo minimal mechanical strains. The major source of micromotion in these implants originates from the sound processor. Therefore, it is crucial that the bone-implant interface is sufficiently osseointegrated before the sound processor of a BAHI is coupled.

Recently, tobacco use has been identified as a major risk factor for failed osseointegration. Evidence shows smoking causes an imbalance in bone turnover, leading to lower bone mass, increasing bone vulnerability to osteoporosis and fractures (Al-Bashaireh et al., 2018). Also, smoking adversely affects hormones and enzymes involved in bone regulation, including parathyroid hormone and alkaline phosphatase. Tobacco smoke has over 7,000 chemicals, however, nicotine has been the focus of most research. Nicotine has been shown to have an inhibitory effect on osteogenesis and angiogenesis that play important roles in bone metabolism (Al-Bashaireh et al., 2018). At the cellular level, nicotine reduces the proliferation of red blood cells, macrophages, and fibroblasts and increases micro clot formation in blood vessels through increased platelet adhesiveness (Ghanem et al., 2017). In addition, nicotine stimulates epinephrine and norepinephrine release, which causes vasoconstriction and limits tissue perfusion (Ghanem et al., 2017). An in vivo study in rabbits found nicotine had a dose-dependent inhibitory effect on osteoblast development and on vascular endothelial growth factor, necessary for angiogenesis (Al-

Bashaireh et al., 2018). There are several other chemicals in tobacco, such as polycyclic hydrocarbons and tar, that have also been shown to compromise bone healing in smokers (Ghanem et al., 2017). Chemical polycyclic hydrocarbons such as benzo(a)pyrene can bind to aryl hydrocarbon receptors in osteoblasts and osteoclasts which may have deleterious effects on bone health (Al-Bashaireh et al., 2018). It has been demonstrated that the effect of nicotine on bone healing is more severe in late healing periods than immediately after implantation (Hollinger et al., 1999). It is possible that peripheral vasoconstriction and down-regulation of osteoblastic activity caused by nicotine, can contribute to late implant failure.

Both Larson et al. and Tjellstrom et al. each presented implant loss in heavy smokers. In addition to smoking, one patient was diabetic and the other was on oral steroid medications (Larsson et al., 2015; Tjellstrom et al., 2007). The aforementioned are known risk factors for failed osseointegration. It is possible a synergetic event took place resulting in implant loss in these patients. Similar to our case, these patients experienced delayed healing and increased pain around the implant site. Also, as reported by our case and others, several 1 implant extrusions in heavy smokers is not uncommon. Processor coupling should be delayed when encountering impeded stability in heavy smokers.

From a clinical perspective, the detrimental effects of tobacco smoking on primary stability and osseointegration cannot be disregarded for auditory osseointegrated implants. In dental literature, smoking has been identified as a major risk factor for implant failure and clinicians recommend a cessation protocol put in place before patients undergo implantation (Bain & Moy, 1993). Smoking cessation seems to reverse the effect of smoking and improve bone health, however, research is still being conducted to quantify the reversal effects (Al-Bashaireh et al., 2018).

CONCLUSION

Successful osseointegration is a prerequisite for functional bone anchored hearing implants. Smoking has been shown to have a major impact on primary stability and osseointegration. This case report and review of literature demonstrates the risks associated with bone anchored hearing implant loss and smoking. Consideration should be given when implanting BAHIs in heavy smokers.

ACKNOWLEDGMENTS

The authors acknowledge Taline Ekmekjian, MLIS and the staff at the McConnell Resource Centre of the McGill University Health Centre for creating the search strategies used for the literature review.

REFERENCES

Al-Bashaireh, A. M., Haddad, L. G., Weaver, M., Chengguo, X., Kelly, D. L., & Yoon, S. (2018). The Effect of Tobacco Smoking on Bone Mass: An Overview of Pathophysiologic Mechanisms. *J Osteoporos, 2018*, 1206235. doi:10.1155/2018/1206235

Bain, C. A., & Moy, P. K. (1993). The association between the failure of dental implants and cigarette smoking. *Int J Oral Maxillofac Implants, 8*(6), 609-615.

Bess, F. H., & Humes, L. (2008). *Audiology: the fundamentals*. Philadelphia.

Biskobing, D. M. (2002). COPD and osteoporosis. *Chest, 121*(2), 609-620.

Esposito, M., Hirsch, J. M., Lekholm, U., & Thomsen, P. (1998). Biological factors contributing to failures of osseointegrated oral implants. (I). Success criteria and epidemiology. *Eur J Oral Sci, 106*(1), 527-551.

Gelfand, S. A. (2009). Essentials of audiology. *New York: Thiem*.

Ghanem, A., Abduljabbar, T., Akram, Z., Vohra, F., Kellesarian, S. V., & Javed, F. (2017). A systematic review and meta-analysis of pre-clinical studies assessing the effect of nicotine on osseointegration. *Int J Oral Maxillofac Surg, 46*(4), 496-502. doi:10.1016/j.ijom.2016.12.003

Hollinger, J. O., Schmitt, J. M., Hwang, K., Soleymani, P., & Buck, D. (1999). Impact of nicotine on bone healing. *J Biomed Mater Res, 45*(4), 294-301.

Hudspeth, A. J. (1989). How the ear's works work. *Nature, 341*(6241), 397-404. doi:10.1038/341397a0

Hudspeth, A. J. (1992). Hair-bundle mechanics and a model for mechanoelectrical transduction by hair cells. *Soc Gen Physiol Ser, 47*, 357-370. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1369770

Kanis, J. A., Johnell, O., Oden, A., Johansson, H., De Laet, C., Eisman, J. A., . . . Tenenhouse, A. (2005). Smoking and fracture risk: a meta-analysis. *Osteoporos Int, 16*(2), 155-162. doi:10.1007/s00198-004-1640-3

Kasat, V., & Ladda, R. (2012). Smoking and dental implants. *Journal of International Society of Preventive & Community Dentistry, 2*(2), 38-41. doi:10.4103/2231-0762.109358

Larsson, A., Tjellstrom, A., & Stalfors, J. (2015). Implant losses for the bone-anchored hearing devices are more frequent in some patients. *Otology & Neurotology, 36*(2), 336-340. doi:https://dx.doi.org/10.1097/MAO.0000000000000446

Lustig, L. R., Arts, H. A., Brackmann, D. E., Francis, H. F., Molony, T., Megerian, C. A., . . . Niparko, J. K. (2001). Hearing rehabilitation using the BAHA bone-anchored hearing aid: Results in 40 patients. *Otology & Neurotology, 22*(3), 328-334. doi:Doi 10.1097/00129492-200105000-00010

Mavrogenis, A. F., Dimitriou, R., Parvizi, J., & Babis, G. C. (2009). Biology of implant osseointegration. *J Musculoskelet Neuronal Interact, 9*(2), 61-71.

Musiek, F. E., Weihing, J. A., & Oxholm, V. B. (2007). *Anatomy and physiology of the Central Auditory Nervous System: A Clinical Perspective*. New York: Thieme.

Parithimarkalaignan, S., & Padmanabhan, T. V. (2013). Osseointegration: an update. *Journal of Indian Prosthodontic Society, 13*(1), 2-6. doi:10.1007/s13191-013-0252-z

Raphael, Y., & Altschuler, R. A. (2003). Structure and innervation of the cochlea. *Brain Res Bull, 60*(5-6), 397-422. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12787864

Salvi, R., Sun, W., & Lobarinas, E. (2007). *Anatomy and Physiology of the Peripheral Auditory System.*

Sayardoust, S., Omar, O., Norderyd, O., & Thomsen, P. (2018). Implant-associated gene expression in the jaw bone of smokers and nonsmokers: A human study using quantitative qPCR. *Clinical Oral Implants Research, 29*(9), 937-953. doi:10.1111/clr.13351

Singh, J. A., Schleck, C., Harmsen, W. S., Jacob, A. K., Warner, D. O., & Lewallen, D. G. (2015). Current tobacco use is associated with higher rates of implant revision and deep infection after total hip or knee arthroplasty: a prospective cohort study. *BMC Med, 13*, 283. doi:10.1186/s12916-015-0523-0

Tjellstrom, A., Granstrom, G., & Odersjo, M. (2007). Survival rate of self-tapping implants for bone-anchored hearing aids. *Journal of Laryngology & Otology, 121*(2), 101-104.

LINKING STATEMENT

Investigating reason behind implant losses would benefit the auditory implant community to better their candidacy selection process and, when encountering an extrusion, to discover possible reasons why this occurred. Chapter 3 examined auditory implant stability and osseointegration and showed that there is an urgent need of an objective way to determine the integrity of the bone-implant interface.

Over the last decade, the percutaneous bone anchored hearing system has seen many design improvements and surgical innovations. Improved surgical approaches successfully decreased operative time and peri-operative complications, while wider screws with roughened surfaces demonstrated improved implant stability. These changes have resulted in lower implant loss rates (Johansson et al., 2017; Verheij et al., 2016; Shah et al., 2016). The next chapter investigates innovations in surgical approaches to bone anchored hearing implant placement.

Chapter 4

Innovations of outcomes and surgical approaches

A Systematic Review on Complications of Tissue Preservation Surgical Techniques in Percutaneous Bone Conduction Hearing Devices

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Published in: Otology & Neurotology 2016 Aug;37(7):829-37.

ABSTRACT

Objective: To investigate skin-related postoperative complications from tissue preservation approaches in percutaneous bone conduction device (BCD) implantations.

Data sources: PubMed, Embase and Cochrane Library.

Study selection: We identified studies on BCDs including the opted surgical technique and derived complications. Retrieved articles were screened using pre-defined inclusion criteria. Critical appraisal included directness of evidence and risk of bias. Studies that successfully passed critical appraisal were included.

Data extraction: Outcome measures included patient demographics, surgery time, follow-up time and complications reported by Holgers' classification.

Data synthesis: We selected 18 articles for data extraction; encompassing 356 BCDs implanted using non-skin thinning approaches. Four studies reported an implantation technique using the punch method (81 implants), 13 studies applied the linear incision technique without soft tissue reduction (288 implants) and one study used the Weber technique (12 implants). Holgers' 3 was described in 2.5% following the punch technique, in 5.9% following the linear incision technique and in no implants following the Weber technique. Overall, one patient was mentioned having Holgers' 4 and skin overgrowth was reported in six patients and. Ten studies compared their non-skin thinning technique to a skin thinning technique. Overall, the soft tissue preservation technique had a similar or superior complication rate, shorter surgical time and better and faster healing, compared to the soft tissue reduction technique.

Conclusion: Tissue preservation surgical techniques for percutaneous BCDs have limited postoperative skin complication rates. Moreover, these techniques are suggested to have at least similar complications rates compared to skin thinning techniques.

Keywords: Bone conduction, percutaneous, complications, operative time, Holgers'classification.

INTRODUCTION

Percutaneous bone conduction hearing devices (BCD) can partially restored hearing in patients with single sided deafness or conductive/mixed hearing loss not benefitting from a conventional air conduction hearing device. The device consists of a titanium fixture inserted in the mastoid bone with a skin-penetrating abutment where a sound processor is coupled.[1,2] BCDs utilize the natural bone transmission as a pathway for sound to travel to the inner ear and sensed by the cochlea, bypassing the external auditory canal and middle ear.[3]

Nowadays, most procedures occur in a single-stage procedure where placement of the fixture and abutment are implanted during the same surgical intervention. In the less common two-stage procedure, the fixture is implanted and the abutment is placed in a second surgical setting. The decision for one or two step primarily depends on the thickness of the skull.[2,4] As such, in pediatric patients the skull can be thin, therefore the fixture needs time to osseointegrate before the abutment can be placed.[2,4] For both techniques, the standard surgical procedure includes thinning of the skin around the implant. This is done to assure tight contact between skin and bone tissue in order to avoid mobility and overgrowth of the skin surrounding the abutment and diminishing the risk of infections.[1,2,5-7] Adverse skin reactions around the implant are the most frequently reported complications following percutaneous BCD implantation.[6,8,9] In recent clinical series evaluating outcomes of percutaneous BCDs, a 23.9% complication rate was reported (i.e. adverse skin reactions or infections).[10] When skin related problems are minor, a conservative treatment such as silver nitrate, steroid or antibiotic ointment has proven effective.[10,11]

The Holgers' classification is used to describe soft tissue reactions consisting of grades 0 (no reaction) to 4 ("removal of skin-penetrating implant necessary due to infection").[6]

Throughout the years, various surgical techniques have been developed attempting to minimize complications. [1,9, 12-14] To date, the single linear incision technique is advocated as the most promising.[1,9, 12-14] With the introduction of longer abutments the possibility to implant without soft tissue reduction while also maintaining optimal stability has been suggested.[15, 16] It is estimated that without skin thinning, less surgical trauma and a smaller risk of devascularization will occur. This will consequently lead to faster healing with less skin complications.[17-20]

The present review aims to investigate skin-related postoperative complications of tissue preservation surgical techniques in percutaneous BCD implantations.

METHODS

Search strategy

We performed a comprehensive search in PubMed, Embase and Cochrane Library from inception until November 3rd, 2015. Search terms were "bone conduction device", "skin thinning", as well as "complications" and all synonyms. See appendix 1 for a complete overview. The search was updated on March 10th 2016.

Study selection

We screened all retrieved articles for title and abstract. Articles on BCDs in children or adults were selected. We excluded non-human studies, articles in languages other than English or Dutch. Subsequently, we screened articles for full text. Studies with a non-retrievable full texts were excluded. We considered letters, commentaries, case reports, editorials, posters not eligible. When the same population or data was presented in more than one publication, we selected only the most comprehensive or most recent. Only studies that opted for a non-skin thinning technique were included.

Quality assessment

We critically appraised all eligible articles for directness of evidence (DoE) and risk of bias (RoB) by predefined criteria. DoE was assessed using six criteria; study population, indication for surgery, surgical procedure, outcome measures on complications and per surgical technique and follow-up. RoB was assessed using standardization of surgical procedure, standardization of skin-related outcomes using Holgers' classification, missing data and standardization of follow-up.
The DoE assessment was scored as high in articles where positive scores were attained on five or six criteria, as moderate in articles with positive scores on four criteria, and as low in articles with

positive scores on less than four criteria. When the complication rated could not be extracted per surgical technique (criteria complications per surgical technique), the article scored low on DoE (Table 1). The RoB assessment was scored as low in articles where positive scores were attained on three or four criteria, and as high in articles with positive scores on less than three criteria. Articles scoring high (H) or medium (M) for directness of evidence and low (L) for risk of bias were included for data extraction (Table 1).

Data extraction

After critical appraisal we extracted data from the included studies. Demographic data such as gender, age at implantation and indication for surgery were extracted. The number and degree of postoperative skin-related complications reported by the Holgers' classification and other complications were the primary outcomes. Surgical time was also extracted as secondary outcome parameter.

Table 1. Critical Appraisal of selected studies

			Directness of evidence (DoE)							**Risk of bias (RoB)**					
	Publication year	**Study design**	**Study population**	**Indication for surgery**	**Surgical procedure**	**Outcome measure on complications**	**Complications reported per surgical technique**	**Follow-up**	**DoE score**	**Standardization of surgical procedure**	**Standardization of reported complications**	**Missing data**	**Standardization of follow up**	**RoB score**	**Passed critical appraisal**
Altuna *et al* [19]	2014	PCS	●	○	●	●	●	◑	M	◑	●	●	◑	L	Yes
Amonoo *et al* [21]	2015	PCS	●	●	●	●	○	◑	L	○	●	●	◑	L	No
den Besten *et al* [22]	2016	PCS	●	●	●	●	●	◑	H	●	●	●	●	L	Yes
Brant *et al* [23]	2013	RCS	●	○	●	●	●	○	M	●	○	●	◑	L	Yes
Calvo Bodnia *et al* [24]	2014	RCS	●	●	●	●	○	◑	L	◑	●	●	◑	L	No
Carr *et al* [25]	2014	RCS	●	●	●	●	●	◑	H	◑	○	●	◑	H	No
Dumon *et al* [26]	2015	PCS	●	●	●	●	●	◑	H	●	●	●	◑	L	Yes
Goldman *et al* [20]	2013	RCS	●	●	●	●	●	◑	H	◑	●	●	◑	L	Yes
Gordon *et al* [27]	2015	RCS	●	●	●	●	●	◑	H	●	●	●	◑	L	Yes
Hawley *et al* [28]	2013	RCS	●	○	●	●	●	○	M	●	●	●	◑	L	Yes
Høgsbro *et al* [29]	2015	RCT	●	●	●	●	●	●	H	●	●	●	●	L	Yes
Hultcrantz [16]	2015	PCS	●	●	●	●	●	●	H	●	●	●	●	L	Yes
Hultcrantz *et al* [30]	2014	RCS	●	●	●	●	●	●	H	●	●	●	●	L	Yes
Husseman *et al* [31]	2013	PCS	●	●	●	●	●	○	H	◑	●	●	◑	L	Yes
Iseri *et al* [32]	2015	RCS	●	●	●	●	●	●	H	◑	●	●	○	L	Yes

Jarabin *et al* [17]	2014	PCS	●	●	●	●	●	○	H	○	●	●	●	L	Yes
Lanis *et al* [33]	2013	RCS	●	●	●	●	●	●	H	●	●	●	●	L	Yes
Martínez *et al* [34]	2015	PCS	●	●	●	●	●	●	H	●	●	●	●	L	Yes
Singam *et al* [35]	2014	PCS	●	○	●	●	●	●	H	●	●	●	◑	L	Yes
Wilkie *et al* [36]	2014	PCS	●	●	●	●	●	◑	H	●	●	●	◑	L	Yes
Wilson *et al* [37]	2013	RCS	●	●	●	●	●	●	H	◑	●	●	●	L	Yes

Study design: Retrospective case study (RCS), Prospective case study (PCS), Randomized controlled trial (RCT)

Directness of evidence (DoB):
Study population (age at surgery, gender*)*: complete ●, not reported ○
Indication for surgery: clearly reported and complete●, clearly reported but incomplete ◑ not clearly reported ○
Surgical procedure: clearly reported ●, not clearly reported ○
Outcome measures on complications: clearly reported ●, not clearly reported ○
Complications per surgical technique: ● complications reported per surgical technique, ◑ complications not reported per surgical technique, but complications on non-skin thinning and skin thinning separately reported, ○ complications not reported per surgical technique and non-skin thinning and skin thinning techniques not separately reported
Follow-up: minimum of ≥1 year ●, minimum of ≥6months and < 1year ◑, minimum of <6months or not reported ○

DoE score: High (H) ≥ 5 points, Medium (M) ≥4 <5 points, Low (L) <4 points. NB: when ○ on complications per surgical technique: Low (L)

Risk of Bias (RoB):
Standardization of surgical procedure: the same technique in the same cohort by the same team●, the same technique in the same cohort but not by the same team ◑ different techniques or not specified ○
Standardization of skin related outcomes using Holgers' classification: clearly reported per surgical technique ●, not clearly reported per surgical technique ○
Missing data: no missing data or missing data mentioned/quantified and method of handling described ●, missing data mentioned in study but method of handling not described ◑, missing data not reported ○
Standardization of follow-up: identical length of follow up for all patients ●, reported however length not identical ◑, not reported ○

RoB score: Low (L) >2 points, High (H) ≤2 points

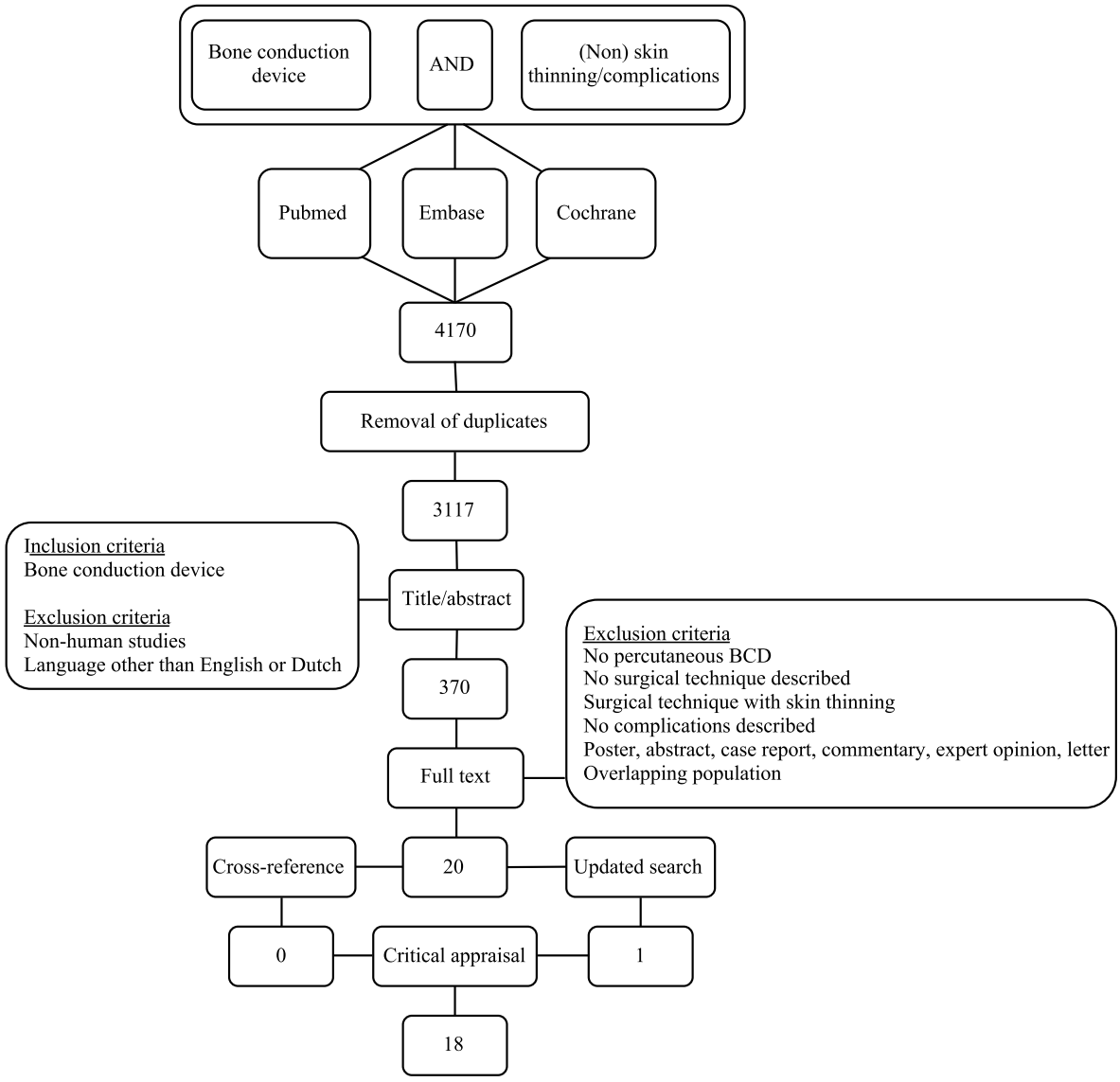
Article passes when H or M on DoB and L on RoB

RESULTS

Search results and critical appraisal

Figure 1 demonstrates the study selection process. A total of 4170 articles were identified by our search; 3117 were unique. After screening for title and abstract we reviewed 370 articles for full text. Cross-reference checking resulted in no additional articles. We selected twenty articles for critical appraisal from which 17 articles successfully passed quality assessment (Table 1). The updated search on March 10th 2016 retrieved one additional article, which also passed critical appraisal.[22] In total, 18 articles were included for data extraction. There was one randomized controlled trial (RCT) where linear incision technique without soft tissue reduction was compared to the dermatome technique with soft tissue reduction.[29] All other studies were prospective or retrospective case studies.[16,17,19-28,30-37] Ten of the 18 studies (including the RCT) compared their non-skin thinning technique with a skin thinning technique. The skin-thinning techniques differed from linear incision technique, (U-shaped) dermatome technique, inverted-J technique to skin flap technique. [17,22,23,26,27,29,30,33,34,37].

Figure 1. Flow chart demonstrating study selection process



Patient characteristics

The included studies encompassed 380 patients and 381 implants. 78% of patients were adults, 4% pediatric and in 18% age was not clearly stated in the included articles. Table 2 summarizes demographic data extracted from the 18 articles. Overall mean age of patients was 51.3 years (range 6-85.7). The 9 mm abutment was most commonly used (See table 2). Indications for surgery were single sided deafness (n=68), sensorineural hearing loss (n=4), mixed hearing loss (n=65) or conductive hearing loss caused by different etiologies (n=66). One article grouped acquired mixed and conductive hearing loss together (n=21).[22] There were four studies using the punch technique (n=81)[20,26,27,31], 13 studies opting for a linear incision technique without soft tissue reduction (n=288)[16,17,19, 22, 28-36] and one study using the Weber technique (n=12)[23]. All studies except for two used a single stage approach. [28,33]

Table 2. Summary of patient and implant characteristics

	Included, n (%)
n, total patients	
Total	380
Adult	296 (78)
Child	17 (4)
N/A	67 (18)
n, total implants	381
Age at implantation, in years	
Mean (range)	51.3 (6-85.7) *(from 17 studies)*
N/A	30 patients
Gender	
Male	162 (43)
Female	213 (56)
N/A	5 (1)
Indication for implantation	
Single sided deafness	68 (18)
Mixed HL	65 (17)
Ear atresia	15 (4)
Ear canal stenosis	1 (0)
Conductive HL	13 (3)
Conductive/Mixed HL	21 (6)
Sensorineural HL	4 (1)

HL from cholesteatoma	18 (5)
HL from chronic otitis media	13 (3)
HL from otosclerosis	1 (0)
Congenital malformation	5 (1)
N/A	156 (41)
Brand of device used	
Oticon	81 (21)
Cochlear	119 (31)
N/A	181 (48)
Abutment size	
5.5mm	4 (1)
6mm	13 (3)
8mm	19 (5)
8.5mm	64 (17)
9mm	152 (40)
10mm	26 (7)
12mm	34 (9)
N/A	69 (18)

Abbreviations: Not Available (N/A), Hearing loss (HL)

Skin-related complications; Holgers' 3 and 4

All studies reported skin complications using the Holgers' classifications. Table 3 shows all complications reported during 762 observations. It should be noted that some studies reported several observations from the same patient, while other studies reported only the worst Holgers' grade per patient, which in table 3 is noted as one observation per patient.

Holgers' 3 was described in 3 out of 137 observations (2.2%) (probably 2 out of 81 implants (2.5%), since the two observations of Holgers' 3 by Gordon et al. were made in the same implant, confirmed with author[27]) using the punch technique, in 17 out of 288 implants (5.9%) using the linear incision technique without skin thinning and in none of the 12 implants using the Weber technique. In the linear incision group 8 out of 17 patients reported by Hawley et al. might have had skin overgrowth (included in Holgers' 3), whereas other studies reported skin overgrowth separately (not Holgers' classification).[28] Husseman et al. described two patients with Holgers'

3. Although both experienced recurrences of infection they responded well to conservative care with silver nitrate and antibiotics.[31] Martínez et al. presented a patient with Holgers' 3 one week after surgery. Complete resolution was noted at the one month postoperative evaluation.[34] Den Besten et al. reported on three patients with Holgers' 3, all responded well to local treatment.[22] The treatment or healing time was not described in the remaining patients with Holgers' 3.
Only Hawley et al. reported a patient with Holgers' 4. This patient was younger than 10 years and implanted in two stages using the linear incision technique. [28]

Implant extrusion not resulting from adverse skin reactions

Eight additional cases of implant extrusion was reported, not classified as Holgers' 4.[16,27,29,31-33] Gordon et al. described one patient with an implant extrusion before the first postoperative visit, the patient was re-implanted and graded as a Holgers' 0 at first visit.[27] Iseri et al. included one patient requiring implant explantation due to pain.[32] Lanis et al. described one abutment loss, however the reason was not elucidated. Lanis et al. also observed a lack of osseointegration in one patient, leading to fixture loss.[33] Hogsbro et al. reported a patient requiring removal of the implant due to reasons not related to skin complications.[29] Hultcrantz et al. and Husseman et al. described a total of three non-users resulting in the removal of the abutment.[30,31]

Skin overgrowth

Skin overgrowth was reported in six patients.[16,19,23,30,37] Hawley et al. classified skin overgrowth as Holgers' 3.[28] Therefore, the numbers of patients with skin overgrowth in the aforementioned study could not be extracted. Moreover, six of their included patients needed soft tissue revision with at least one soft tissue overgrowth. Indications for the other five patients were

not described. It also remained unclear whether all patients who required soft tissue revision were classified as Holgers' 3.[28]

Of the six patients with soft tissue overgrowth reported in the other studies, one patient was treated successfully with topical treatment.[19] A patient with skin overgrowth received a longer abutment,[36] and four patients received skin excision [16,23,37] (one patient is mentioned twice; receiving skin excision and a longer abutment)[37]. Finally, the treatment modality for one patients with skin overgrowth was not described.[30]

Surgical time

Surgical time was reported in 12 out of 18 studies (Table 3). Shortest surgical time was described by Hultcrantz, with a mean time of 12.4 minutes.[16] The Weber technique used by Brant et al. took the longest with a mean duration of 39 min per surgery, however there was one outlier (88 minutes). Without this patient, the mean surgical time would decrease to 34 min (SD 12).[23]

Table 3. Outcomes per surgical technique of included studies

Surgical technique	Number of implants	Study	Mean surgical time in minutes (range)	Mean follow-up time in months (range)	Skin related complications; Holgers' grade, absolute number of observations						Other complications (n)
					Time point	0	1	2	3	4	
Punch	81	Dumon *et al* [26]	15 (15-25)	10.5 (6-18)	≤ 6 months	32	4	6			
					≥ 6 months	12	2	3			
		Goldman *et al** [20]	15.2 (13-18)	14.8 (9-20)	Mean 14.8 months		15				
		Gordon *et al* [27]	13.4 (7-34)	10 (0.25-25)	≤1 week*	12	3	1	1		Implant extrusion (1)
					≤ 25 months*	13	2	1	1		
		Wilson *et al** [37]	32.3 (SD 9.6)	≥12	≥12 months	24	1	3	1		Skin overgrowth (1)
Linear incision without soft tissue reduction	263	Altuna *et al* [19]	21 (15-35)	≥6	≤ 3 week	57	6	4			Skin overgrowth (1)
					≥12 weeks	68					
		den Besten *et al** [22]	20.8 (13-29)	6	≤6 months	11	7	4	3	0	
		Hawley *et al** [28]	?	18.5 (3-45)	Mean 18.5 months	22	3	3	8**	1	Skin overgrowth (?)
		Høgsbro *et al* [29]	?	12	≤ 1 weeks	45	5				Removal of implant (1)
					≤ 6 months	12 9	15	2			
					1 year	23					
		Hultcrantz *et al** [30]	?	60	≤ 5 years	4	6	1	1		Removal of abutment (1) Skin overgrowth (1)
		Hultcrantz* [16]	12.4	12	≤ 1 year	9		1			Skin overgrowth (1)
		Hussemann *et al** [31]	?	4.9 (1.4-26.2)	Mean 4.9 months	27	2	3	2		Removal of abutment (2)
		Iseri *et al** [32]	19.4 (14-34)	12-16	≤ 16 months	10	3	3			Removal of implant (1)
		Jarabin *et al** [17]	?	4	≤ 4 months	9	1				
		Lanis *et al** [33]	1 step: 34 2 steps: 1st step: 36 2nd step: 33	15.6 (7.2-18)	Mean 15.6 months	7	2		1		Abutment loss (1) Fixture loss (1)
		Martínez *et al* [34]	27 (19-36)	12	≤ 1 week*	0	5	9	1		
					≤ 1 month*	5	8	2			
					≤ 1 year*	11	3	1			
		Singham *et al** [35]	?	Median 23	Median 23 months	25	5				

		Wilkie *et al** [36]	16 (9-22)	8 (6-13)	Mean 8 months	26	2	1	1		
Weber technique	12	Brant *et al** [23]	39 (15-88)	3.25 (SD 4)	Mean 3.25 months	10	2				Skin overgrowth (2), cellulitis (1)

* number of observations equals number of implants, ** included skin overgrowth

Pediatric population

There were three studies in which complication rates of pediatric patients could be extracted. All underwent the linear incision technique[28,32,33]. Lanis et al. included ten children with a mean age of 5.3 (range 2-15) in which surgery was performed in one or two stages. They reported one patient with Holgers' 3, one abutment loss and one fixture loss.[33] Iseri et al. included two pediatric patients aged 6 and 8 years implanted in a single stage. The Holgers' grade for one patient was 0 and 2 for the other.[32] Hawley et al. included five pediatric patients where surgery was performed in two stages in 2 patients. Two of these patients developed Holgers' 3, for which one required soft tissue revision in the operating room and the other patient was treated in a non-operative setting. In addition, one patient suffered from Holgers' 4 and was explanted. The two patients without complications were both older than 16 years.[28]

Timing of complications

Follow-up in patients varied from 13 weeks [23] to 5 years[30] (Table 3). In nine studies timing of complications was reported.[19,26-30,33-35] When presenting the punch technique, one study reported on a slightly lower percentages of Holgers' 2 developed in the first 6 months, compared to complications reported at last follow up (mean 10.5 months) (14.3% and 17.8% respectively).[26] Another study opting the punch technique reported the same number of Holgers' 2 and Holgers' 3 one week postoperative compared to last visit (mean 10 months).[27] Hawley et al. stated that complications occurred between 0.5 and 46 months follow-up, with a mean of 12

months when using the linear incision technique.[28] In addition, Hultcrantz et al. found the time for introduction of first infection sporadically over first three years. This study was the only study with a mean follow-up over two years.[30] Other studies using the linear incision technique did not report on more complications after longer follow-up period. Complications reported by Altuna et al. occurred in the first 4 weeks postoperatively, where 60% of patients were followed for at least one year.[19] In the study by Hogsbro et al. at 10 and 90 days follow-up visits one patient presented with Holgers' 2.[29] Patients of Martínez et al. developed complications mostly within the first week postoperatively. At one year follow-up, there was one patient with Holgers'2 (7%).[34]

DISCUSSION

This review aimed to elucidate skin-related complications arising from tissue preservation surgical approaches in percutaneous BCD implantation. All studies revealed that tissue preservation techniques are safe with a low incidence of postoperative infections in short and long term follow-ups. Different non-skin thinning techniques such as the punch technique, linear incision technique without soft tissue reduction and the Weber technique are described. Holgers' 3 was described in 2 out of 81 implants (2.5%) using the punch technique[20,26,27,37], in 17 out of 288 implants (5.9%) using the linear incision technique without skin thinning [16,17,19,28-36] and in none of the 12 implants using the Weber technique[23]. Only one Holgers' 4 out of a total of 356 implants was described. This patient was younger than 10 years and operated on using the linear incision technique without soft tissue reduction in two stages.[28]

Skin overgrowth was reported in at least six patients. [16,19,23,30,37] In addition, Hawley et al. described six patient who required soft tissue revision. Although the indication for revision

was not mentioned it is likely that for the majority of these patients soft tissue overgrowth was the reason for soft tissue revision.[28]

No intraoperative complications were reported. The major drawback of the punch technique is the limited visualization. However, Dumon et al. reported adequate visualization by soft tissue mobilization.[26]

Overall, included studies suggest that there is less surgical trauma and better vascularization in skin preservation techniques. In turn, this leads to fewer adverse skin reactions, thus, less infections.[16,19,20,29,31,33] This is supported by the study of Jarabin et al. where Laser Doppler Flowmeter with and without heat provocation tests were used to assess microcircular patterns. Their conclusion was that after the linear incision technique without soft tissue reduction more viable regeneration processes of microcirculation were observed around the implant compared to skin reduction technique (U-shaped dermatome technique).[17]

Pediatric population

Children have a greater risk of developing adverse soft tissue reactions after implantation of a BCD compared to adults.[4,11] This might be due the greater challenges in regular daily skin care around the abutment.[4] Concordantly, in the presented review outcomes, the only Holgers' 4 was encountered in a pediatric patient.[28] Nonetheless, Lanis et al. have found a low skin-related complication rate in their pediatric cohort.[33] Overall, the pediatric patient group derived from this review, was too small to draw general conclusions from the included studies.

Timing of complications

Timing of complications differs greatly among included studies.[19,26-30,33-35]. In the study with the longest follow-up period, infections appeared sporadically in the first three years after implantation.[30] Follow-up periods of other studies might not be sufficiently long enough

(< 3 years).[19,26,27,29,34] The peak of complication rate also remains unclear, varying between a mean of 12 months postoperatively [28] to the first weeks or months after implantation.[19,29,34]

Comparison with soft tissue reduction techniques

Out of the 18 included studies, ten studies compared soft tissue preservation technique with a skin thinning technique which included the linear incision technique, the (U-shaped) dermatome technique, inverted-J technique and skin flap technique.[17,22,23,26,27,29,30,33,34,37] In two studies the skin preservation technique was the same as the skin reduction technique, without skin thinning.[22, 34] All authors of studies included in this review, concluded that the soft tissue preservation technique had similar or superior outcomes compared to the soft tissue reduction technique. Outcome measures included better or similar complication rates and shorter surgical time.[17,22,23,26,27,29,30,33,34,37] However, Den Besten et al. reported more skin related complications in the linear incision technique without soft tissue reduction group compared to the linear incision technique with soft tissue reduction group. Yet, these complication responded well to local treatment.[22] In addition, some articles reported better and faster postoperative healing [26,29,33], less postoperative numbness and pain [22,29,30] and better cosmetic results[22,26,27,30,33] in the skin preservation technique compared to the skin reduction technique.

Regarding the literature on skin-thinning techniques, many different techniques with varying outcomes are reported.[8,9,13] Kiringoda et al. described 20 articles using various skin thinning techniques in a systematic review on complications after BCD implantation.[8] A distinction was made in an adult or mixed adult/pediatric population and a pediatric population. Adverse skin reaction classified by Holgers' were separately reported from infections around the

implant depending on how the original article reported on complications.[8] The authors found a Holgers' 3 incidence of between 0.6 to 14.3% and a Holgers' 4 rate of between 0.4 to 4.8% in the adult or mixed population. In the pediatric population no studies using the Holgers' classification were included. Peri-implant infection rates ranged from 1 to 50% in the adult and mixed population and 5.6-44% in the pediatric population. Soft tissue overgrowth requiring soft tissue excision was found in 8.4-9.4% in the adult and mixed population and 10-22.2% in the pediatric population.[8] The current review did not make a distinction in adult or pediatric population nor did the included articles separate adverse skin reactions from peri-implant infections. However, our reported complication rate and skin overgrowth rate is similar to the findings reported by Kiringoda et al. Concerning skin overgrowth, it is important to note that that Kiringoda et al. only reported on skin overgrowth requiring soft tissue excision[8]. The present review included only four patients (overall percentage of 1.3%) required requiring soft tissue excision (excluding Hawley et al. who reported on six patients requiring soft tissue revision for possible different indications[28]). These numbers suggest tissue preservation techniques to be more optimal in terms of skin overgrowth.

In addition, a retrospective case study by Dun et al. investigated 1132 percutaneous bone conduction implants.[11] In 108 implants the skin graft technique was applied and in 1024 various incision techniques involving skin thinning. Most commonly, the Nijmegen linear incision technique was opted.[11] In total, 7415 observations were done during follow-up. Holgers' 3 was observed in 1.0% and Holgers' 4 in 0.2%. Implant loss or elective removal was observed in 8.3%. Most implants were lost in the first 12 months after surgery and revision surgery was performed in 6.6% of cases. Indications for these were skin overgrowth in the majority of implants, fitting a new abutment or exploration of implant site due to pain or unsuccessful wound healing.[11] The incidences reported by Dun et al. are reported in number per observations, while in many of the

included studies in this review, incidences are reported in number per implants. When a complication is temporary (which is expected for Holgers' 3) the incidence per observations would likely be lower than the incidence per implant. After all, multiple observations (with and without complications) are made in one implant.

Due to these different reporting styles, incidences reported by Dun et al. are difficult to compare to the incidences reported by the included studies in this review. Despite this, the present review did report a higher percentage of Holgers' 3 compared to Dun et al. Hawley et al. reported a rate of 22% of Holgers' 3 by including skin overgrowth, probably leading to a significant higher incidence rate.[28]

Overall, although the complication rates vary considerably among different studies on skin-thinning techniques (due to different techniques and outcome parameters), the complication risk of non-skin thinning techniques appears to be at least similar compared to skin-thinning techniques. This is especially true when taking into account the articles that compared skin thinning with a non-skin thinning technique.

Limitations

Our main limitation is that most of the studies were retrospective cohort studies, and only one RCT was included.[28] Moreover, the results were not homogenous since different techniques were opted, not only different tissue preservation techniques but also different techniques in control groups if present. Also, various outcome parameters were studied, in particular the use of reported outcome per observation versus the reported outcome per patient. Therefore no statement could be made on which technique, skin preservation or skin reduction, or which technique of all skin preservation techniques, is superior.

CONCLUSION

Skin preservation surgical techniques for percutaneous BCDs have limited postoperative skin complication rates. When they do occur, complications are often mild in severity. In addition the skin preservation surgical techniques require less surgical time compared to the classical skin thinning techniques. There is evidence that fast healing, lower pain and numbness with a good cosmetic result are facilitated by this approach.

REFERENCES

1. Cass SP, Mudd PA. Bone-anchored hearing devices: Indications, outcomes, and the linear surgical technique. *Oper. tech. otolaryngol.--head neck surg.* 2010;21(3):197-206

2. Tjellström A, Håkansson BO, Granström G. Bone-anchored hearing aids: Current Status in adults and children. *Otolaryngol Clin North Am.* 2001;34(2):337-364

3. Reinfeldt S, Håkansson B, Taghavi H, Eeg-Olofsson M. New developments in bone-conduction hearing implants: a review. *Med Devices (Auckl)*. 2015;16(8):79-93.

4. Roman S, Nicollas R, Triglia JM. Practice guidelines for bone-anchored hearing aids in children. *Eur Ann Otorhinolaryngol Head Neck Dis.* 2011;128(5):253-8.

5. Proops DW. The Birmingham bone anchored hearing aid programme: Surgical methods and complications. *J Laryngol Otol*. 1996;110(Suppl 21):7-12

6. Holgers KM, Tjellstrom A, Bjursten LM, Erlandsson BE. Soft tissue reactions around percutaneous implants: a clinical study of soft tissue conditions around skin-penetrating titanium implants for bone-anchored hearing aids. *Am J Otol*. 1988; 9:56–9

7. Reyes RA, Tjellström A, Granström G. Evaluation of implant losses and skin reactions around extraoral bone-anchored implants: A 0- to 8-year follow-up. *Otolaryngol Head Neck Surg* 2000;122:272-6

8. Kiringoda R, Lustig LR, A Meta-analysis of the Complications Associated With Osseointegrated Hearing Aids. *Otol Neurotol.* 2013;34(5):790-4.

9. Mohamad S, Khan I, Hey SY, Hussain SSM. A systematic review on skin complications of bone-anchored hearing aids in relation to surgical techniques. *Eur Arch Otorhinolaryngol.* 2016;273(3):559-65.

10. Hobson JC, Roper AJ, Andrew R, Rothera MP, Hill P and Green KM. Complications of bone-anchored hearing aid implantation. *J Laryngol Otol*. 2010;124:132-136.

11. Dun CAJ, Faber HT, de Wolf MJF, Mylanus EAM, Cremers CWRJ and Hol MKS. Assessment of more than 1,000 implanted percutaneous bone conduction devices: Skin reactions and implant survival. *Otol Neurotol.* 2012;33(2):192-8.

12. Fontaine N, Hemar P, Schultz P, Charpiot A, Debry C. BAHA implant: Implantation technique and complications. *Eur Ann Otorhinolaryngol Head Neck Dis.* 2014;131(1):69-74.

13. van de Berg R, Stokroos RJ, Hof JR, Chenault MN. Bone-anchored hearing aid: A comparison of surgical techniques. *Otol Neurotol.* 2010;31(1):129–135.

14. de Wolf MJF, Hol MKS, Huygen PLM, Mylanus EAM, Cremers CWRJ. Clinical outcome of the simplified surgical technique for BAHA implantation. *Otol Neurotol.* 2008;29(8):1100-1108.

15. Høgsbro M, Agger A, Vendelbo Johansen L. Successful loading of a bone-anchored hearing implant at two weeks after surgery: randomized trial of two surgical methods and detailed stability measurements. *Otol Neurotol*. 2015;36(2):e51-7.

16. Hultcrantz M. Stability Testing of a Wide Bone-Anchored Device after Surgery without Skin Thinning. *BioMed Res Int.* 2015;2015. ArticleID:853072

17. Jarabin J, Bere Z, Hartmann P, Tóth F, Kiss JG and Rovó L. Laser-Doppler microvascular measurements in the peri-implant areas of different osseointegrated bone conductor implant systems. *Eur Arch Otorhinolaryngol.* 2015;272(12):3655-62.

18. Hultcrantz M. Outcome of the bone-anchored hearing aid procedure without skin thinning: a prospective clinical trial. *Otol Neurotol*. 2011;32(7):1134-1139.

19. Altuna X, Navarro JJ, Palicio I, Alvarez L. Bone-anchored hearing device surgery: Linear incision without soft tissue reduction. A prospective study. *Acta Otorrinolaringol Esp.* 2015;66(5):258-263.

20. Goldman RA, Georgolios A, Shaia WT. The punch method for bone-anchored hearing aid placement. *Otolaryngol Head Neck Surg.* 2013;148(5):878-880.

21. Amonoo-Kuofi K, Kelly A, Neeff M, Brown CRS. Experience of bone-anchored hearing aid implantation in children younger than 5 years of age. *Int J Pediatr Otorhinolaryngol.* 2015;79(4):474-80.

22. den Besten CA, Bosman AJ, Nelissen RC, Mylanus EAM, Hol MKS. Controlled clinical trial on bone-achored hearing implants and a surgical technique with soft tissue preservation. *Otol Neurotol.* 2016 Mar 3. [Epub ahead of print]

23. Brant JA, Gudis A, Ruckenstein MJ. Results of Baha® implantation using a small horizontal incision. *Am J Otolaryngol.* 2013;34(6):641-5.

24. Calvo Bodnia N, Foghsgaard S, Nue Møller M, Cayé-Thomasen P. Long-term results of 185 consecutive osseointegrated hearing device implantations: a comparison among children, adults, and elderly. *Otol Neurotol.* 2014;35(10):301-6.

25. Carr SD, Moraleda J, Baldwin A, Ray J. Bone-conduction hearing aids in an elderly population: complications and quality of life assessment. *Eur Arch Otorhinolaryngol.* 2016;273(3):567-71.

26. Dumon T, Medina M, Sperling NM. Punch and Drill: Implantation of Bone Anchored Hearing Device Through a Minimal Skin Punch Incision Versus Implantation With Dermatome and Soft Tissue Reduction. *Ann Otol Rhinol Laryngol.* 2016;125(3):199-206.

27. Gordon SA, Coelho DH. Minimally invasive surgery for osseointegrated auditory implants: A comparison of linear versus punch techniques. *Otolaryngol Head Neck Surg.* 2011;152(6):1089-93.

28. Hawley K, Haberkamp TJ. Osseointegrated hearing implant surgery: Outcomes using a minimal soft tissue removal technique. *Otolaryngol Head Neck Surg.* 2013;148(4):653-7.

29. Høgsbro M, Agger A, Vendelbo Johansen L. Bone-anchored hearing implant surgery: randomized trial of dermatome versus linear incision without soft tissue reduction-clinical measures. *Otol Neurotol.* 2015;36(5):805-11.

30. Hultcrantz M, Lanis A. A five-year follow-up on the osseointegration of bone-anchored hearing device implantation without tissue reduction. *Otol Neurotol.* 2014;35(8):1480-5.

31. Husseman J, Szudek J, Monksfield P, Power D, O'Leary S and Briggs R. Simplified bone-anchored hearing aid insertion using a linear incision without soft tissue reduction. *J Laryngol Otol.* 2013;127(Suppl 2):33-38

32. Iseri M, Orhan KS, Yariktaș MH et al. Surgical and audiological evaluation of the Baha BA400. *J Laryngol Otol.* 2015;129(1):32-7.

33. Lanis A, Hultcrantz M. Percutaneous osseointegrated implant surgery without skin thinning in children: a retrospective case review. *Otol Neurotol.* 2013;34(4):715-22.

34. Martínez P, López F, Gómez JR. Cutaneous complications in osseointegrated implants: Comparison between classic and tissue preservation techniques . *Acta Otorrinolaringol Esp.* 2015;66(3):148-53.

35. Singam S, Williams R, Saxby C, Houlihan FP. Percutaneous bone-anchored hearing implant surgery without soft-tissue reduction: up to 42 months of follow-up. *Otol Neurotol.* 2014;35(9):1596-600.

36. Wilkie MD, Chakravarthy KM, Mamais C, Temple RH. Osseointegrated hearing implant surgery using a novel hydroxyapatite-coated concave abutment design. *Otolaryngol Head Neck Surg.* 2014;151(6):1014-9.

37. Wilson DF, Kim HH. A minimally invasive technique for the implantation of bone-anchored hearing devices. *Otolaryngol Head Neck Surg.* 2013;149(3):473-7.

LINKING STATEMENT

Since the publication of the systematic review in 2016, more and more implant centers globally have implemented skin preservation approaches to bone anchored hearing implant surgery. When bone anchored hearing implants were first presented, it was done in 2 stages; one to place the implant screw, and the other to place the abutment. Skin reduction was also done to supposedly reduce skin related complications. Since then, single stage procedures and skin preservation during surgery have been implemented.

These ultimately reduce surgical duration by limiting the need of unnecessary procedure and risks associated with these and anesthesia exposure. Innovations in surgical approaches have also aided this cause. These are further discussed in the next chapter.

4.2 Response to letter

Response to Comment on "A Systematic Review on Complications of Tissue Preservation Surgical Techniques in Percutaneous Bone Conduction Hearing Devices"

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Published in: Otology & Neurotology 2017 Jan;38(1):158-159.

LETTERS TO THE EDITOR

Comment on "A Systematic Review on Complications of Tissue Preservation Surgical Techniques in Percutaneous Bone Conduction Hearing Devices"

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Otology & Neurotology: January 2017 - Volume 38 - Issue 1 - p 157-158

To the Editor: With great interest we read the recently published systematic review by Verheij et al. [(1)] reviewing skin-related postoperative complications of tissue preservation surgical techniques in percutaneous bone conduction hearing devices implantation. A total of 18 studies were included in data extraction, of which 10 studies who compared a number of non-skin-thinning techniques with several skin-thinning techniques. Most important outcomes were the number and degree of postoperative skin-related complications reported by the Holgers' classification [(2)] and other clinical complications such as skin overgrowth and implant extrusion not resulting from adverse skin reactions. We highly support the initiative for writing this systematic review regarding tissue preservation techniques and the review gives a good overview of all studies on tissue preservation to date. On the other hand, we would like to discuss some of our concerns since several factors influencing skin-related complications were not addressed.

In the review, to start with, no distinction is made between different types of abutments, i.e., the part of the implant in direct contact with the skin. All different currently available abutments were included in the review, amongst others the previous generation BA210, and more recently developed BA300 (all Cochlear BAS, Sweden) and Ponto (standard and wide implants) (Oticon Medical, Sweden). It has been shown in a long-term follow-up study that the BA300 implant with all titanium abutment resulted in significantly less Holgers 2 or higher skin reactions

compared with the also all titanium BA210, using an identical skin-thinning technique [3]. On the contrary, the new BA400 is not all-titanium but has a hydroxyapatite-coating and is designed to prevent skin overgrowth and trapping of debris, therefore, hypothesized to reduce soft tissue reactions. However, it could be argued that these abutments have an even greater tendency to develop biofilms due to pathogenic micro-organisms on the hydroxyapatite surface [4]. A prospective comparative clinical trial, assessing incidence and severity of adverse skin-related complications for both abutments, i.e., all-titanium versus coated, using the same surgical technique, is lacking. Therefore, differences in (currently) available abutments could influence outcome and should, therefore, be mentioned.

Another factor that has not been addressed in the review is abutment length. Before the introduction of non-skin-thinning techniques it has been shown that in implantation with skin-thinning immediate use of an 8.5 mm abutment, instead of a 5.5 mm abutment, decreases postoperative rates of infection, skin overgrowth, and need for revision surgery due to wound complications [5]. In addition, studies that used the 8.5-mm abutment after failure of the 5.5-mm abutment, have shown to be successful in preventing the need for additional surgical intervention in most patients with postoperative soft tissue overgrowth [6,7]. Since the introduction of non-skin-thinning techniques, abutments up to 12 mm are available nowadays. Although no studies have assessed the impact of abutment length in this technique, it clearly indicates that abutment length should be mentioned as possible factor influencing skin-related complications apart from the surgical technique used.

The authors conclude that tissue preservation surgical techniques are suggested to have at least similar complications rates compared with skin-thinning techniques, based on 10 studies who compared a soft tissue preservation technique with a skin-thinning technique. However, eight of these comparative studies use a less than ideal control-group, including dermatome technique, inverted-J technique, and skin flap technique or test-groups with a variation on the preservation technique, like a (modified) punch technique [8–15]. Hence, by comparing groups with two or more differing variables, i.e., different incision technique and either skin reduction or preservation, no conclusions can be made on the impact of tissue preservation alone. Only the studies by den Besten et al. [16] and Martinez et al. [17] compare groups with identical linear incision techniques, therefore, both groups only differed in tissue preservation or reduction. This was mentioned briefly in the discussion by Verheij et al. [1], however, we think that this is key in the results and should be emphasized in interpretation of the overall conclusions. Martinez et al. [17] showed that, although the Holgers' grade was always worse in the standard technique (Holgers' score 3 was 28% versus 7% at 1 wk), the complication rate was not statistically significant between the two groups at any time during follow-up. den Besten et al. [16], however, reported more skin-related complications in the soft tissue preservation group compared with the soft tissue reduction group after 6 months follow-up. Conclusive evidence and long-term follow-up are lacking, therefore, currently no firm conclusions can be drawn regarding the effect on skin-related complications by the technique tissue preservation alone.

Reference

1. Verheij E, Bezdjian A, Grolman W, et al. A systematic review on complications of tissue preservation surgical techniques in percutaneous bone conduction hearing devices. *Otol Neurotol* 2016; 37:829–837.
2. Holgers KM, Tjellstrom A, Bjursten LM, et al. Soft tissue reactions around percutaneous implants: a clinical study of soft tissue conditions around skin-penetrating titanium implants for bone-anchored hearing aids. *Am J Otol* 1988; 9:56–59.
3. den Besten CA, Stalfors J, Wigren S, et al. Stability, survival, and tolerability of an auditory osseointegrated implant for bone conduction hearing: long-term follow-up of a randomized controlled trial. *Otol Neurotol* 2016; 37:1077–1083.
4. Larsson A, Wigren S, Andersson M, et al. Histologic evaluation of soft tissue integration of experimental abutments for bone anchored hearing implants using surgery without soft tissue reduction. *Otol Neurotol* 2012; 33:1445–1451.
5. Allis TJ, Owen BD, Chen B, et al. Longer length Baha abutments decrease wound complications and revision surgery. *Laryngoscope* 2014; 124:989–992.
6. Monksfield P, Ho EC, Reid A, et al. Experience with the longer (8.5 mm) abutment for bone-anchored hearing aid. *Otol Neurotol* 2009; 30:274–276.
7. Pelosi S, Chandrasekhar SS. Soft tissue overgrowth in bone-anchored hearing aid patients: use of 8.5 mm abutment. *J Laryngol Otol* 2011; 125:576–579.
8. Gordon SA, Coelho DH. Minimally invasive surgery for osseointegrated auditory implants: a comparison of linear versus punch techniques. *Otolaryngol Head Neck Surg* 2015; 152:1089–1093.

9. Hawley K, Haberkamp TJ. Osseointegrated hearing implant surgery: outcomes using a minimal soft tissue removal technique. *Otolaryngol Head Neck Surg* 2013; 148:653–657.

10. Hogsbro M, Agger A, Johansen LV. Bone-anchored hearing implant surgery: randomized trial of dermatome versus linear incision without soft tissue reduction—clinical measures. *Otol Neurotol* 2015; 36:805–811.

11. Hultcrantz M, Lanis A. A five-year follow-up on the osseointegration of bone-anchored hearing device implantation without tissue reduction. *Otol Neurotol* 2014; 35:1480–1485.

12. Singam S, Williams R, Saxby C, et al. Percutaneous bone-anchored hearing implant surgery without soft-tissue reduction: up to 42 months of follow-up. *Otol Neurotol* 2014; 35:1596–1600.

13. Husseman J, Szudek J, Monksfield P, et al. Simplified bone-anchored hearing aid insertion using a linear incision without soft tissue reduction. *J Laryngol Otol* 2013; 127:S33–S38.

14. Hultcrantz M. Stability testing of a wide bone-anchored device after surgery without skin thinning. *Bio Med Res Int* 2015; 2015:853072.

15. Jarabin J, Bere Z, Hartmann P, et al. Laser-Doppler microvascular measurements in the peri-implant areas of different osseointegrated bone conductor implant systems. *Eur Arch Otorhinolaryngol* 2015; 272:3655–3662.

16. den Besten CA, Bosman AJ, Nelissen RC, et al. Controlled clinical trial on bone-anchored hearing implants and a surgical technique with soft-tissue preservation. *Otol Neurotol* 2016; 37:504–512.

17. Martinez P, Lopez F, Gomez JR. Cutaneous complications in osseointegrated implants: comparison between classic and tissue preservation techniques. *Acta Otorrinolaringol Esp* 2015; 66:148–153.

Response to Comment on "A Systematic Review on Complications of Tissue Preservation Surgical Techniques in Percutaneous Bone Conduction Hearing Devices"

With great interest we read the letter to the editor regarding our systematic review on skin-related postoperative complications of tissue preservation techniques in percutaneous bone conduction hearing device implantation. The overall conclusion of our systematic review was that complications after tissue preservation techniques are limited and that these techniques may have some important advantages such as fast healing and lower pain and numbness (1). The authors of the letter raised important points and concerns regarding our review.

First, the authors addressed the lack of emphasis on studies comparing a skin preservation technique with a skin reduction technique in our review. We agree that ideally a study comparing techniques varying only in skin reduction or preservation is most valuable. However, the impact of tissue preservation compared with tissue reduction technique was not the scope of our review. Our aim was to assess the safety of the preservation of tissue during a bone conduction device implantation.

Secondly, the authors of the letter mentioned that our review did not make a distinction between different abutments, in type or in length. We did not include this in our data analysis because it falls out of the scope of our review. However, we agree that different types or lengths of abutments could influence postoperative outcomes. Unfortunately, most authors we reviewed varied the length of abutment according to each patient's need (2–15). In addition, in seven of our included studies the type of abutment was not mentioned (1,7,8,12,15–17). Furthermore, (a selection of) patients in the studies by Dumon et al. (5), Iseri et al. (10), Jarabin et al. (11), and Wilkie et al. (14) were implanted with a hydroxyapatite-coated abutment. As mentioned by the authors of the letter to the editor, a hydroxyapatite coating is argued to lead to less or to more

postoperative skin related complications. However, the studies in our review which included patients with a hydroxyapatite-coated abutment did not change our conclusion.

Overall, our included articles are heterogeneous, and therefore prevented us from pooling data and calculating a risk of postoperative complications. Nevertheless, our conclusion that tissue preservation techniques in implanting bone conduction devices are safe is supported by our systematic review. For future perspectives, we would like to conduct a prospective comparative study with a long-term follow-up, to compare different tissue preservation techniques.

REFERENCE

1. Verheij E, Bezdjian A, Grolman W, Thomeer HGXM. A systematic review on complications of tissue preservation surgical techniques in percutaneous bone conduction hearing devices. Otol Neurotol 2016; 37:829–837.

]2. Altuna X, Navarro JJ, Palicio I, Alvarez L. Bone-anchored hearing device surgery: Linear incision without soft tissue reduction. A prospective study. Acta Otorrinolaringol Esp 2015; 66:258–263.

3. Brant JA, Gudis A, Ruckenstein MJ. Results of Baha® implantation using a small horizontal incision. Am J Otolaryngol 2013; 34:641–645.

4. den Besten CA, Bosman AJ, Nelissen RC, Mylanus EAM, Hol MKS. Controlled clinical trial on bone-achored hearing implants and a surgical technique with soft tissue preservation. Otol Neurotol 2016; 37:504–512.

5. Dumon T, Medina M, Sperling NM. Punch and drill: implantation of bone anchored hearing device through a minimal skin punch incision versus implantation with dermatome and soft tissue reduction. Ann Otol Rhinol Laryngol 2016; 125:199–206.

6. Goldman RA, Georgolios A, Shaia WT. The punch method for bone-anchored hearing aid placement. Otolaryngol Head Neck Surg 2013; 148:878–880.

7. Hawley K, Haberkamp TJ. Osseointegrated hearing implant surgery: outcomes using a minimal soft tissue removal technique. Otolaryngol Head Neck Surg 2013; 148:653–657.

8. Hultcrantz M, Lanis A. A five-year follow-up on the osseointegration of bone-anchored hearing device implantation without tissue reduction. Otol Neurotol 2014; 35:1480–1485.

9. Hultcrantz M. Stability testing of a wide bone-anchored device after surgery without skin thinning. Biomed Res Int 2015; 2015:853072.

10. Iseri M, Orhan KS, Yariktaş MH, et al. Surgical and audiological evaluation of the Baha BA400. J Laryngol Otol 2015; 129:32–37.

11. Jarabin J, Bere Z, Hartmann P, Tóth F, Kiss JG, Rovó L. Laser-Doppler microvascular measurements in the peri-implant areas of different osseointegrated bone conductor implant systems. Eur Arch Otorhinolaryngol 2015; 272:3655–3662.

12. Lanis A, Hultcrantz M. Percutaneous osseointegrated implant surgery without skin thinning in children: a retrospective case review. Otol Neurotol 2013; 34:715–722.

13. Singam S, Williams R, Saxby C, Houlihan FP. Percutaneous bone-anchored hearing implant surgery without soft-tissue reduction: up to 42 months of follow-up. Otol Neurotol 2014; 35:1596–1600.

14. Wilkie MD, Chakravarthy KM, Mamais C, Temple RH. Osseointegrated hearing implant surgery using a novel hydroxyapatite-coated concave abutment design. Otolaryngol Head Neck Surg 2014; 151:1014–1019.

15. Wilson DF, Kim HH. A minimally invasive technique for the implantation of bone-anchored hearing devices. Otolaryngol Head Neck Surg 2013; 149:473–477.

16. Husseman J, Szudek J, Monksfield P, Power D, O'Leary S, Briggs R. Simplified bone-anchored hearing aid insertion using a linear incision without soft tissue reduction. J Laryngol Otol 2013; 127:33–38.

17. Høgsbro M, Agger A, Vendelbo Johansen L. Bone-anchored hearing implant surgery: randomized trial of dermatome versus linear incision without soft tissue reduction-clinical measures. Otol Neurotol 2015; 36:805–811.

LINKING STATEMENT

The published article (now cited 35 times) has confirmed the idea that skin reduction does not benefit the post-operative skin healing and reduce the likelihood of skin reaction. Since its publication, more and more centers across the world are opting for skin preservation during surgery. This reduces significantly the duration of surgery. Moreover, novel surgical approaches were presented where skin reduction is not performed. The next study compares this novel approach with the commonly performed linear surgery technique without skin reduction in a clinical cohort.

4.3 Comparing two surgical approaches

Experience with Minimally Invasive Ponto Surgery and Linear Incision Approach for Pediatric and Adult Bone Anchored Hearing Implants

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Published in: Ann Otol Rhinol Laryngol. 2020 Apr;129(4):380-387.

ABSTRACT

Purpose: To compare intra- and post-operative outcomes between the standard linear incision with tissue preservation and the Minimally Invasive Ponto Surgery (MIPS).

Study Design: A non-randomized prospective cohort series

Methods: Medical files were reviewed of adult and pediatric bone anchored hearing implant recipients. Extracted outcomes included patient characteristics, implant survival, operative time, anesthesia use, intra and post-operative complications, soft tissue tolerability assessed by the Holger's classification, and implant stability assessed by the Resonance Frequency Analysis (RFA). Outcomes were compared between two surgeries.

Results: A total of 59 implants were placed (21 MIPS; 38 linear). Conductive hearing loss was the most common etiology for implantation. Surgery was conducted under local anesthesia in 67% of MIPS patients and 16% of linear patients. No intra-operative complications were reported for both surgical approaches and no implants were lost. Patients undergoing implantation via the MIPS approach displayed less skin reaction post-operatively. The median and mean surgical duration for the MIPS group was statistically lower than the linear group (P = .0001). Implant stability measured by the RFA implant stability quotient was greater in the MIPS cohort.

Conclusion: The MIPS approach seems either similar or superior to the linear approach in all peri-operative outcomes evaluated. Outcomes such as surgical duration, anesthesia choice and implant stability measurements support implantation through the MIPS approach for patients meeting eligibility criteria.

Keywords: bone anchored hearing implant, BAHA, bone conduction, MIPS.

BACKGROUND

Osseointegrated bone anchored hearing implants (BAHIs) were first described in the 1970s. Since then, these implantable systems have rehabilitated hearing-impaired adults and children with success rates of 90% or higher [1-4]. BAHIs rely on the transmission of sound via bone conduction that is sensed by the inner ear. These devices are comprised of an external sound processor, which is coupled to a titanium fixture implanted into the temporoparietal skull region behind the ear.

The percutaneous BAHI has seen many enhancements since the first reported case [1]. Novel surgical approaches successfully decreased operative duration and peri-operative complications, while wider screws with roughened surfaces improved the stability of the bone-implant interface [5-8]. Ultimately, these innovations resulted in lower incidences of implant failures, increased overall satisfactory rates, and allowed early sound processor coupling protocols that shortened the detrimental period of auditory deprivation.

Of these surgical innovations, the Minimally Invasive Ponto Surgery (MIPS) technique developed by Oticon Medical AB (Askim, Sweden) promotes BAHI placement under local anesthesia [9]. This “punch only” approach is conducted in a single-stage procedure that aims to reduce surgical time and variability, alleviate the need for an incision scar, and minimize trauma to the bone and soft tissue [10-11]. Early evidence evaluating peri-operative outcomes of the MIPS technique suggests a favorable operative time, few intra-operative complications, rapid healing, and satisfactory results regarding soft tissue tolerability and implant survival. Nonetheless, the novel approach presents with challenges pertaining to the visibility of the implantation site due to its non-invasive cannula guided approach.

The objective of the current study was to compare peri-operative outcomes of the MIPS technique and the linear incision approach in a prospective cohort series of adult and pediatric BAHI recipients.

MATERIALS AND METHODS

Study Design

This prospective cohort study is a non-randomized clinical comparison of outcomes via two surgical approaches to BAHI surgery. The study was approved by McGill University Health Centre Research Ethics Board (ref # 2018-3444).

Description of Surgical Procedures

All implantations were performed by the same surgeon (S.J.D.). Peri-operative implant stability quotient (ISQ) scores and soft tissue tolerability was evaluated by a nurse clinician (M.B) and was categorized using the Holger's classification [12]. Two different surgical approaches were used for implantation: linear incision technique and MIPS [9,13]. Prior to surgery, anesthesia feasibility and benefits were discussed and a joint decision between the surgeon, patient and/or parent was reached.

Linear incision technique (with soft tissue preservation)

Since 2010, several groups have reported improved tolerance to percutaneous devices implanted without reduction of the soft tissues surrounding the percutaneous abutment [6]. Therefore, implantation through a linear incision without soft tissue reduction as described by Hultcrantz was performed [13]. A retroauricular linear incision was made down to the periosteum. Subcutaneous tissue was dissected for exposure and mobilization of the periosteum at the intended implant site. This was followed by the drilling procedure with saline irrigation for cooling, with

subsequent widening using a countersink drill as described by Tjellstrom and Granstrom [14]. The implant with a mounted abutment was installed. The skin was repositioned over the abutment and a hole was punched in the skin overlying the abutment. The incision was closed with interrupted sutures. Non-adherent dressing soaked with antibiotic ointment was wrapped around the abutment and a healing cap was attached.

Minimally Invasive Ponto Surgery (MIPS)

MIPS is a minimally invasive approach described by Johansson et al. For this procedure, the implant site was located using a sound processor indicator [9]. Once the skin thickness was measured, a 5-mm circular punch was made, and the bone was exposed. Guided by a protective cannula to avoid soft tissue trauma, drilling was performed with copious cold irrigation to prevent heat-induced trauma and widening was performed. The implant screw, with abutment, was inserted. Non-adherent dressing soaked with antibiotic ointment was placed around the abutment and a healing cap was attached.

Study Population and Outcome Measures

Data was extracted from a prospectively collected database of BAHI recipients from May 2013 to December 2018 (linear incision approach) and from November 2015 to December 2018 (MIPS). Pediatric and adult patients were included. Extracted data included patient demographics (age at intervention, gender, laterality of implant), operative information (use of anesthesia, operative time, screw, initial stability, and screw and abutment characteristics) and post-operative outcomes (soft tissue integrity, ISQ, and implant survival). The defined surgical time was the period between the procedure start and end times recorded on the intra-operative record.

Assessment of Soft Tissue Tolerability

Tolerability of the soft tissue surrounding the implant site was monitored and classified according to the Holger's classification [12]. The classification system grades soft tissue reactions at the implant site in regard to redness, swelling, moistness, and granulation tissue.

Measurement of Implant Stability Quotient

All included patients had an intra-operative and at least one post-operative ISQ measurement to assess implant stability. Implant stability was evaluated via the resonance frequency analysis (RFA) model introduced by Meredith et al. to clinically test implant stability in a non-invasive manner [15]. The instrument measures the resonance frequency in hertz and translates it into a clinically useful score classified through the ISQ scale ranging from 1 to 100. A higher ISQ score correlates with a more stable implant. Measurements are conducted in 2 perpendicular directions resulting in a high and low ISQ value [16]. To analyze the ISQ data, raw ISQ scores were used to display overall mean progression or regression of implant stability. However, since abutment type and length influences ISQ scores, threshold shifts from the intra-operative baseline score were calculated to account for the effect of implant-specific differences.

Statistical Analysis

The distribution of continuous data was presented using graphs with error bars that allowed for a comparison of the differences between the means within the groups (ISQ scores). When the data were not distributed normally, medians and ranges were added to present the continuous data adequately (age). Categorical data were summarized using percentages (gender, indication for surgery, skin tolerability). Differences in baseline characteristics between the cohorts and peri-operative outcomes were tested using the non-parametric, independent-sample Mann–Whitney U tests for continuous variables and the Fisher's exact tests for categorical variables. P-values below 0.05 were considered statistically significant.

RESULTS

Patient demographics

Included in this study were 59 BAHIs placed in 52 patients. 21 surgeries were performed through the MIPS technique and 38 surgeries used the linear incision approach. There were 7 patients implanted bilaterally, all through the linear incision approach. In the MIPS cohort, the gender distribution was equal, while in the linear incision cohort, 17 patients (55%) were male while 14 (45%) were female. There was no statistically significant gender-specific differences identified between both cohorts. Mean and median ages at the time of surgery were 40.4 and 47 years, and 16 and 8 years, for the MIPS and linear cohorts respectively (Table 1). Differences in age were significantly different between the two cohorts ($p = 0.001$). Thus, patients who underwent implantation through the linear incision technique were significantly younger.

Most patients presented with conductive hearing loss (8 in MIPS and 20 in linear group). These included conditions such as aural atresia, microtia, cholesteatoma, and middle ear damage. The underlying etiology for implantation were sensorineural hearing loss in 5 MIPS patients and 3 linear incision patients. There was no significant difference with regards to the laterality of the implants placed.

Table 1. Patient Characteristics

	MIPS	**LINEAR**
N, implants	21	38
N, patients	21	31
Gender		
Male	9 (42.8 %)	17 (54.8 %)
Female	9 (42.8 %)	14 (45.2%)
NS	3 (14.2 %)	0
Mean age at surgery [range] (years)	40.43 [14 - 70]	16 [4 - 63]
Median age at surgery (years)	47	8
Type of hearing loss		
CHL	8	20
SNHL	5	3
Mixed HL	0	2
Other	1	0
NS	7	6
Implant laterality		
Left	10 (47.6 %)	9 (29.0 %)
Right	10 (47.6 %)	15 (48.4 %)
Bilateral	0	7 (22.6 %)
NS	1 (4.8 %)	0

Anesthesia and surgery duration

In the MIPS cohort, 14 patients (66.7%) opted for local anesthetic with IV sedation while 5 patients (23.8%) underwent surgery with general anesthesia. In the linear incision cohort, 21 patients (67.7%) underwent general anesthesia surgery while 5 (16.1%) opted for local anesthesia (Table 2).

Table 2. Surgical Outcomes

	MIPS	**LINEAR**
Mean surgical procedure time	29 min	1h, 9 min
Range	14 min – 1h, 5min	34 min – 2h, 10 min
Anesthesia		
Local with sedation	14 (66.7%)	5 (16.1%)
General	5 (23.8%)	21 (67.7%)
NS	2 (9.5%)	5 (16.2%)
ISQ scores		
# of pts	17	8
Mean baseline high	50.7	44.1
Mean baseline low	47.1	41.5

The mean surgical time in the linear incision cohort was 1 hour and 9 minutes (range, 34 – 130 mins) versus 29 minutes for the MIPS cohort (range, 14 – 65 mins). The shortest surgery was performed in 14 minutes in a patient undergoing MIPS with local anesthesia and sedation. Box-plots showing the median surgical duration in minutes for both groups show longer surgical time for the linear group (Figure 1).

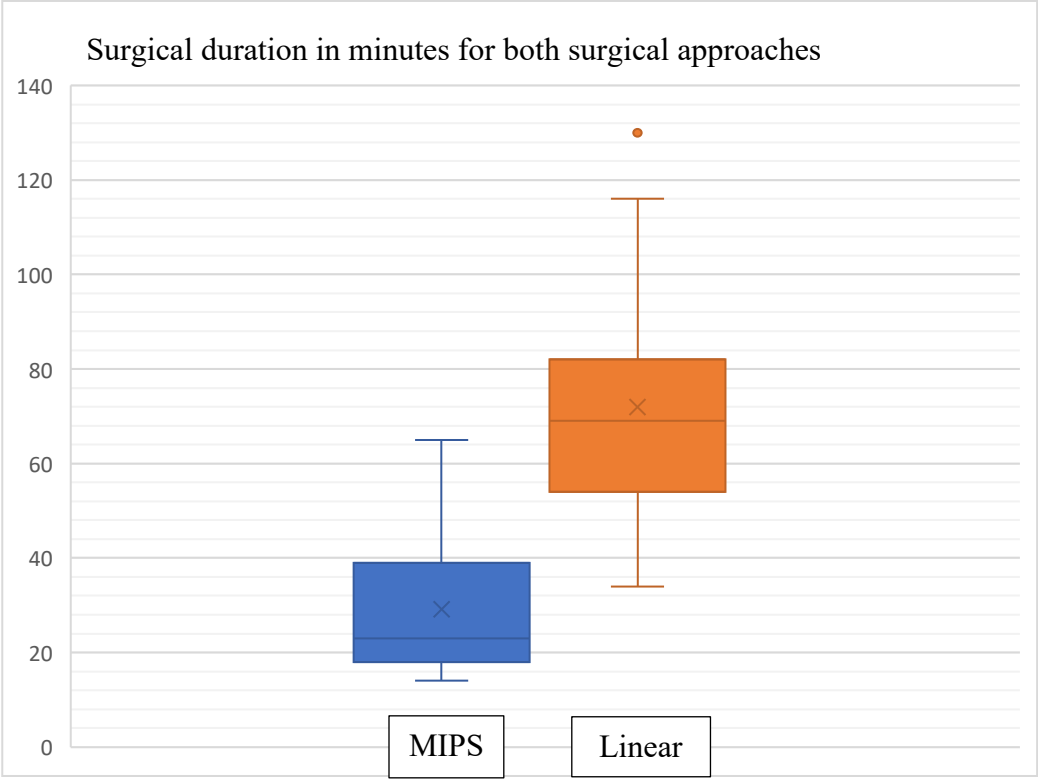


Figure 1. Surgical Duration. Box-plots showing the median surgical duration in minutes for the MIPS group and the linear group. This difference was statistically significant ($P = .0001$).

Skin tolerability

Most observations of soft tissue tolerability showed no irritation (Holger's Grade 0) or slight redness (Holger's Grade 1). Red and slightly moist tissue (Holger's Grade 2) was observed incidentally in both cohorts. There were 5 reports of local reactions corresponding to Holger's Grade 3, of which only one was in a MIPS-implanted patient and four other patients displaying a Holger's Grade 3 skin reaction were implanted via the linear incision approach. Only one linear patient displayed a skin reaction classified as Holger's Grade 4 (Table 3).

Table 3. Skin reaction incidences using Holgers classification observed at follow up visits

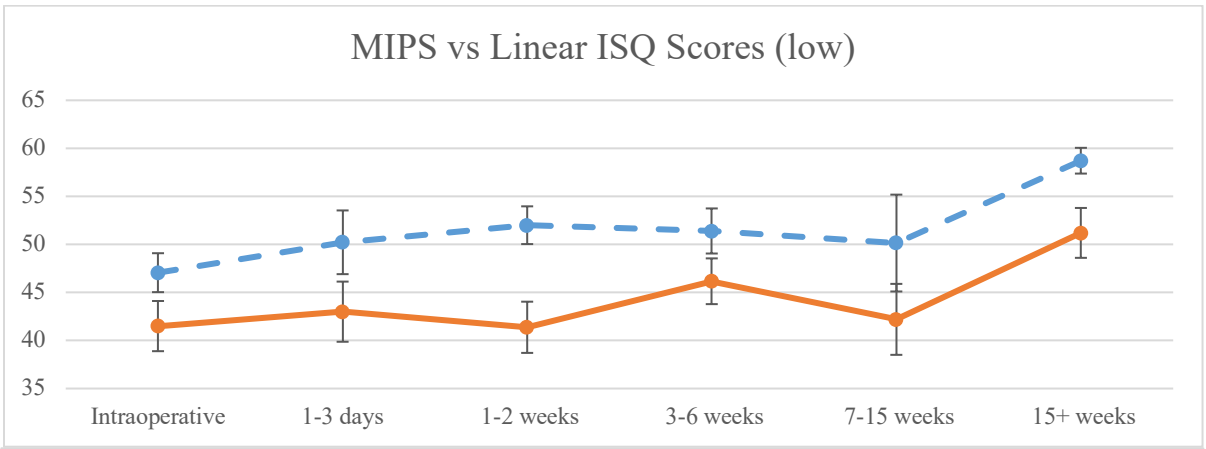
Holgers Classification	*MIPS (n)*	*Linear (n)*	*p **
***Grade 1**: light redness and slight swelling*	26	23	0.2848
***Grade 2**: redness and swelling*	9	9	
***Grade 3**: redness, swelling, moistness, and slight granulation tissue*	1	5	
***Grade 4**: redness, swelling, moistness, granulation tissue, and infection*	0	1	

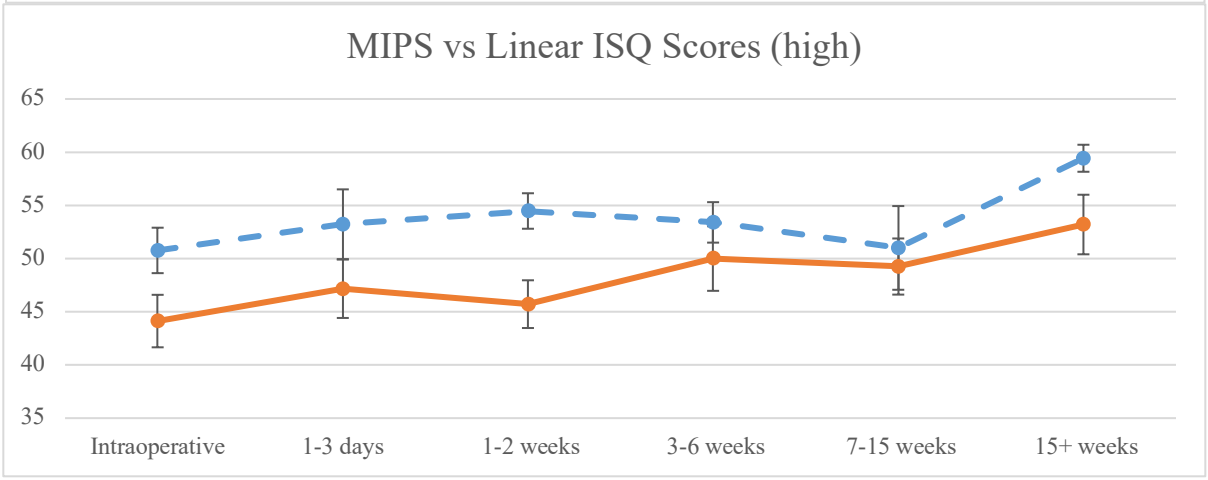
* p value calculated by exact Fisher's showing that differences between surgical approaches are not significant

Implant stability quotient

For the ISQ analysis, 17 MIPS patients and 8 linear patients were included. ISQ low and high scores were consistently superior in the MIPS cohort from intraoperative to over 15 weeks post-operatively (Figure 2a). The mean low ISQ score were 47.1 and 41.5 and the mean high ISQ score were 50.7 and 44.1 in the MIPS and Linear cohorts respectfully (Table 2). Raw ISQ scores were significantly higher in the MIPS cohort at all timepoints tested (Figure 2a). To account for implant size and abutment length differences, threshold shifts were calculated. Intra-operative and early follow-up (1-2 weeks) low and high ISQ scores were significantly higher in the MIPS cohort (Figure 2b) while later time points were indistinguishable between the two methods.

Figure 2a. Peri-operative raw low and high ISQ scores of both surgical approaches


MIPS vs Linear ISQ Scores (low)
65
60
55
50
45
40
35
Intraoperative
1-3 days
1-2 weeks
3-6 weeks
7-15 weeks
15+ weeks


MIPS vs Linear ISQ Scores (high)
65
60
55
50
45
40
35
Intraoperative
1-3 days
1-2 weeks
3-6 weeks
7-15 weeks
15+ weeks

- - - MIPS; – Linear

Figure 2b. Peri-operative low and high ISQ threshold shifts from baseline of both surgical approaches

- - - MIPS; – Linear

DISCUSSION

Bone anchored hearing systems are a successful option in the rehabilitation of hearing-impaired individuals who meet the eligibility criteria. Although novel transcutaneous systems are increasingly gaining popularity, most implant centers around the world perform percutaneous BAHI surgery primarily due to the optimization of sound transfer via direct transmission of sound vibration and the simplicity of the surgery. The BAHI has seen many improvements in recent years involving the design of the implants and the surgical approaches. These innovations aimed to

improve implant stability and overall satisfaction while reducing surgical variability, post-operative complication, and operative time.

Our BAHI cohort included both adult and pediatric patients implanted via two surgical approaches. The linear incision technique is the most commonly performed surgery. In the past, skin reduction was performed around the abutment area in order to reduce skin-related complications. However, recent studies have demonstrated that skin preservation has at least similar complications rates compared with soft tissue reduction techniques [6]. Therefore, implantation without soft tissue reduction is performed in our implant center. The MIPS approach has been recently introduced and claims to reduce surgical time and variability, minimize trauma to the bone and soft tissue as it alleviates the need for an incision [10-11]. This approach was recently introduced in our center.

Anesthesia and surgery duration

The majority of recipients implanted via the MIPS approach opted for local anesthesia with sedation due to the non-invasive nature of the surgery. Surgical duration was the starkest difference when comparing the MIPS and linear incision groups. The mean surgical time of the linear incision procedure was 238% longer than MIPS.

Decreased operative time directly correlates with lower cost for BAHI procedure since it decreases the amount of paid staff time (for surgeons, nurses and anesthesiologists) for each procedure. Sardiwalla et al. conducted a direct cost comparison of minimally invasive punch technique versus traditional approaches for percutaneous bone anchored hearing devices [17]. In their “punch” cohort, all implantations were performed in a clinical setting instead of the operating room. Thus, costs associated with the surgeon, anesthesiologist, nursing staff, hospital resources and equipment were significantly reduced for the MIPS technique.

Prior to surgery, local anesthesia feasibility and benefits were discussed and a joint decision between the surgeon, patient and/or parent was reached. Local anesthesia poses fewer risks than general anesthesia and having this routinely available for a BAHI procedure can be considered an overall safety advantage.

Skin tolerability

The MIPS cohort had overall lower soft tissue complications as assessed by the Holger's classification; fewer grade 3 and 4 reactions. This is expected as no incision in done for this intervention. Soft tissue reactions are commonly associated with implant loss and can cause a delay in processor loading time [18-19]. This delay in implant loading or loss can negatively affect patients' quality of life by delaying hearing rehabilitation until the tissue is healed.

Implant stability quotient

The MIPS cohort had consistently higher ISQ scores intra-operatively and at every follow-up time point. While these scores were consistently higher in the MIPS cohort, raw ISQ data does not consider the lengths and diameter of the implant abutment and screw. Younger patients often require a shorter implant abutment length, thus could demonstrate higher raw ISQ scores. Therefore, threshold shifts are calculated to account for implant specific differences. When threshold shifts were analyzed, recipients implanted through the MIPS often displayed greater threshold shifts, suggesting that there is an overall greater stability with the MIPS approach. However, these findings were not supporting by statistical analysis. The initial stability could be influenced by the MIPS punch technique that allows the surgery to be performed via a cannula. The intact skin could create a cuff of tissue around the implant positively influencing the stability. Further research is needed to assess how the newly introduced ISQ scores are influenced by implant and patient related factors.

Study limitations

The difference in mean patient age between cohorts must be highlighted. No patient below the age of six could be considered a candidate for the MIPS approach at our institution. Therefore, all younger patients underwent BAHI surgery through the linear incision approach. The significant age difference between the two cohorts limits the ability of our study to suggest that the MIPS technique results in greater implant stability based on the ISQ data. Age-dependent differences are important when evaluating BAHI surgeries as implantation outcomes are often influenced by the fact that children have thinner, immature bone; thus, require more time for osseointegration. Hygienic and lifestyle differences could also be attributed to changes in implant stability and skin tolerability in syndromic and pediatric patients in general due to their active lifestyle. The linear incision cohort had a longer follow-up period after implantation, which may have introduced possible reporting bias of the Holger's score since more skin tolerability assessments would have been recorded for these patients. A future improvement of the study is to conduct a prospective cohort consisting of only pediatric or adult patients with standardized follow-up lengths to eliminate potential bias and confounding factors such as patient age.

CONCLUSION

The present cohort study compares two surgical approaches to percutaneous BAHIs. The outcomes reveal that the MIPS approach is either similar or superior to the linear approach in all outcome evaluated. Differences in surgical duration, cost-effectiveness and implant stability measurements support implantation through the MIPS approach for patients meeting eligibility criteria.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Faisal Zawawi and Dr. Lotus Yang for their input in this work.

REFERENCES

1. Tjellström A, Lindström J, Hallén O, Albrektsson T, Brånemark PI. Osseointegrated titanium implants in the temporal bone. A clinical study on bone-anchored hearing aids. *Am J Otol.* 1981;2:304–310.
2. Edmiston RC, Aggarwal R, Green KM. Bone conduction implants - a rapidly developing field. *J Laryngol Otol*. 2015;129(10):936-940.
3. Dun CA, Faber HT, de Wolf MJ, Mylanus EA, Cremers CW, Hol MK. Assessment of more than 1,000 implanted percutaneous bone conduction devices: skin reactions and implant survival. *Otol Neurotol.* 2012;33(2):192-198.
4. Snik AFM, Mylanus EAM, Proops DW, Wolfaardt JF, Hodgetts WE, Somers T, et al. Consensus statements on the BAHA system: where do we stand at present? *Ann Otol Rhinol Laryngol Suppl.* 2005;195:2–12.
5. Johansson ML, Stokroos RJ, Banga R, et al. Short-term results from seventy-six patients receiving a bone-anchored hearing implant installed with a novel minimally invasive surgery technique. *Clin Otolaryngol.* 2016;42(2):1043-1048.
6. Verheij E, Bezdjian A, Grolman W, Thomeer HG. A systematic review on complications of tissue preservation surgical techniques in percutaneous bone conduction hearing devices. *Otol Neurotol.* 2016;37(7):829-837.
7. Hultcrantz M, Lanis A. A five-year follow-up on the osseointegration of bone-anchored hearing device implantation without tissue reduction. *Otol Neurotol* 2014;35(8):1480-1485.

8. Shah FA, Johansson ML, Omar O, Simonsson H, Palmquist A, Thomsen P. Laser-modified surface enhances osseointegration and biomechanical anchorage of commercially pure titanium implants for bone-anchored hearing systems. *PLoS ONE* 2016;11(6):e0157504.
9. Johansson M, Holmberg M. Design and clinical evaluation of MIPS - A new perspective on tissue preservation www.oticonmedical.com. 2015. Accessed on May 12, 2018.
10. Dumon T, Medina M, Sperling NM. Punch and drill: implantation of bone anchored hearing device through a minimal skin punch incision versus implantation with dermatome and soft tissue reduction. *Ann Otol Rhinol Laryngol.* 2015;125:199–206.
11. Gordon SA, Coelho DH. Minimally invasive surgery for osseointegrated auditory implants: a comparison of linear versus punch techniques. *Otolaryngol Head Neck Surg.* 2015;152:1089–1093.
12. Holgers KM, Tjellstrom A, Bjursten LM, Erlandsson BE. Soft tissue reactions around percutaneous implants: a clinical study of soft tissue conditions around skin-penetrating titanium implants for bone-anchored hearing aids. *Am J Otol.* 1988;9(1):56–59.
13. Hultcrantz M. Outcome of the bone-anchored hearing aid procedure without skin thinning: A prospective clinical trial. *Otol Neurotol.* 2011;32:1134-1149.
14. Tjellstrom A, Granstrom G. One-stage procedure to establish osseointegration: a zero to five years follow-up report. *J Laryng Otol* 1995;109:593-598.
15. Meredith N, Alleyne D, Cawley P. Quantitative determination of the stability of the implant-tissue interface using resonance frequency analysis. *Clin Oral Implants Res.* 1996;7:261–267.
16. Nelissen RC, Wigren S, Flynn MC, Meijer GJ, Mylanus EA, Hol MK. Application and interpretation of resonance frequency analysis in auditory osseointegrated implants: A

review of literature and establishment of practical recommendations. *Otol Neurotol.* 2015;36(9):1518-1524.

17. Sardiwalla Y, Jufas N, Morris DP. Direct cost comparison of minimally invasive punch technique versus traditional approaches for percutaneous bone anchored hearing devices. *J Otolaryngol Head Neck Surg.* 2017;46(1):46.
18. Kraai T, Brown C, Neeff M, Fisher K. Complications of bone-anchored hearing aids in pediatric patients. *Int J Pediatr Otorhinolaryngol.* 2011;75(6):749-753.
19. Nelissen RC, Den besten CA, Faber HT, Dun CA, Mylanus EA, Hol MK. Loading of osseointegrated implants for bone conduction hearing at 3 weeks: 3-year stability, survival, and tolerability. *Eur Arch Otorhinolaryngol*. 2016;273(7):1731-1737.

LINKING STATEMENT

As seen in the study, certain outcomes are repeated when it comes to innovating and evaluating the surgeries of bone anchored hearing implants. Of these, skin reactions are often discussed, as it is the most common adverse event observed post-operatively for percutaneous systems. To date, there is no consensus to the way these reactions are identified, classified and treated. The next chapter presents three skin tolerability classification scales and assesses variability in identifying the reactions and treatment outcomes.

Reliability of Post-Surgical Soft Tissue Reaction Grading Scales for Bone Anchored Hearing Implants

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Submitted to: Otology & Neurotology

(revisions submitted)

ABSTRACT

Objective: This study aims to assess and compare the reliability of the Holgers, the IPS and the Tullamore scales for skin tolerability assessment of post-operative bone anchored hearing implant (BAHI) images.

Study Design: A survey study and retrospective review of BAHI images for scoring using three skin classification scales.

Setting: McGill University Health Center, Montreal, Quebec, Canada.

Participants: Healthcare workers experienced and inexperienced with BAHI skin classification scales.

Main Outcome Measure(s): Participation involved completing: 1) survey questionnaires assessing experience with BAHIs and related skin reactions and 2) scoring post-operative BAHI with surrounding skin images using the Holgers Classification, the IS (of the IPS) scale, and the Tullamore Classification. Participants were asked to rate 12 images of post-operative BAHI and surrounding soft tissue. This process was repeated until participants scored all images using the three scales; each rater graded 36 images in total. The order in which scales were presented occurred at random. Intraclass correlation coefficients (ICC) were calculated to assess reliability.

Results: Thirty-one participants were recruited to the study. Fourteen (45.2%) had experience with at least one BAHI skin classification scale, while seventeen (54.8%) did not have experience. The Holgers classification demonstrated the highest interrater reliability (ICC = 0.69 across all raters), particularly for inexperienced raters (ICC = 0.73). The IS (of the IPS scale) had moderate reliability (ICC = 0.65 overall), while the Tullamore classification had the lowest reliability (ICC = 0.60 overall), particularly with inexperienced raters (ICC = 0.49).

Conclusions: The Holgers Classification seems to provide better reliability on reactions post BAHI surgery compared to the IPS and Tullamore, especially amongst inexperienced assessors. Considering the added value of the IPS scale and its interrater reliability, this scale could also be used to assess BAHI skin reactions.

INTRODUCTION

Bone-anchored hearing implants (BAHIs) are a solution for patients with conductive or mixed hearing loss that is not treatable by conventional hearing aids or surgical reconstruction (1,2). The indications for BAHIs include patients with chronic ear infections, acquired canal stenosis or microtia and/or ear canal atresia. The most frequently implanted BAHIs use an osseointegrated percutaneous titanium screw that transmits sound vibrations. The latter are generated by an external auditory processor and are transmitted to the cochlea via the temporal bone. The breach of the skin is the primary factor in the etiology of complications related to percutaneous implants (3,4). In fact, soft tissue reaction is the most commonly observed adverse event and is often caused by bacterial colonization or infection (5). Tissue reactions are influenced by surgery-related factors such as the surgical approach, implant type and location, abutment length and post-operative dressing, or by patient-related factors that influence wound healing, hygiene and self-care such as skin and skull thickness, and comorbidities (6).

The BAHI has undergone many improvements in implant and abutment design to minimize skin reactions. Coated implants, modified abutments, and upgraded surgical techniques have been shown to effectively minimize skin reactions (25,26). Currently, most centers assess skin tolerability post-implantation with the Holgers Classification, which evaluates redness, swelling, moistness and/or granulation around the skin penetrating implant (7). A reliable skin tolerability classification scale is important in the evaluation of post-operative reactions as it allows for delivery of appropriate care and continuity. Having a reliable scale would also be beneficial for the comparison of results between studies. Recently, two new scales have emerged addressing perceived shortcomings of the commonly used Holgers Classification scale: 1) the IPS scale (8),

and 2) the Tullamore Classification (9). An optimal classification tool is short, comprehensible, intelligible, provides clear outcome and reduces subjective variability.

The present study aimed to assess and compare the reliability of the Holgers, the IPS and the Tullamore scales among health care practitioners working in the area of BAHI. Grading soft tissue reactions around the skin-penetrating abutment was achieved using post-surgical BAHI pictures.

METHODS

The study received MUHC Research Ethics Board approval (reference #2019-4776). Audiologists, residents, nurse clinicians, surgeons, and other participants without BAHI experience were approached to participate. Written informed consent was obtained prior to study participation. Participation involved completing : 1) survey questionnaires assessing experience with BAHIs and related skin reactions and 2) scoring post-operative BAHI with surrounding skin images using the Holgers Classification (7), the IPS scale (I for inflammation, P for pain and S for skin height and numbness) (8), and the Tullamore Classification (9) (figure 1-3). Since it is not possible to determine the Pain component of the IPS scale, only the IS were used.

Figure 1. Holgers Classification Scale

Grade 0	No skin reaction
Grade 1	Redness with slight swelling
Grade 2	Redness, moistness, and moderate swelling
Grade 3	Redness, moistness, and moderate swelling, with tissue granulation
Grade 4	Profound signs of infection, resulting in removal of the implant

Figure 2. IS (of the IPS scale)

IS Scale			
Inflammation (Sum of the 4 criteria generating a score from I_0 to I_4)			
Skin integrity?	Erythema (redness)?	Oedema (swelling)?	Granulation tissue formed?
Grade 0 = Intact	Grade 0 = None	Grade 0 = None	Grade 0 = None
Grade 1 = Not intact	Grade 1 = Present	Grade 1 = Present	Grade 1 = Present
Skin height (S_0 to S_2)			
Grade 0	Normal		
Grade 1	Increased, but able to couple sound processor		
Grade 2	Above rim abutment/unable to couple sound processor		

Figure 3. Tullamore Classification scale

Tullamore Classification	
T0	Normal
T^r	Erythema; dry/moist at abutment interface
T1	Excoriation: moist/crusted flat granulation
T2	Heaped granulation
T3	Abutment overgrowth with stable skin

Participants were asked to rate 12 images of post-operative BAHI and surrounding soft tissue. All images showed a BAHI after placement with the linear incision technique. To account for learning affects, participants scored four images at a time using one scale, and then scored the same four images using a different scale. This process was repeated until all participants scored all images on the three scales; each rater graded 36 images in total. The order in which scales were presented occurred at random. Raters had five minutes to familiarize themselves with the grading scales prior to scoring images. Images were displayed on a laptop or computer screen monitor.

Participant raters were blinded to scores of other participants, as well as to patient identity, age and gender, and the time points when the pictures were taken.

Statistical Analysis

Intraclass correlation coefficients (ICC) were calculated to assess reliability. First, different ratings of the same image were compared to the total variation across all ratings and all subjects. The ICC model is used when a sample of judges is selected from a larger population and each judge rates all images (10,11). Higher ICC indicated lower variability. ICC was calculated for each of the three soft tissue reaction grading scales to determine which one manifests less variability amongst raters and therefore produces more reliable ratings. By convention, ICC values ≥ 0.80 are indicative of excellent reliability, between 0.60 and 0.79 of moderate reliability, and less than 0.60 of questionable reliability (10).

RESULTS

BAHI images

All selected images were from follow-up consultations of one to six weeks post-surgery. A total of 12 images were selected showing a post-operative BAHI and surrounding soft tissue. The implant was placed inside the line of incision in five images, while the other seven images displayed an implant outside of the line of incision. Other surgical approaches/features to the surgery varied and were not mentioned. Moreover, the application of tissue preservation or reduction was not stated explicitly.

Participant demographics – survey information

Thirty-one participants were recruited to the study. Fourteen had experience with at least one BAHI skin classification scale, while seventeen did not have experience (Table 1). Those who

had experience with BAHIs were surgeons (n=6), residents (n=5), nurse clinicians (n=1), and researchers (n=2). Surgeons had performed an average of seven BAHI surgeries per year and were familiar with the Holgers Classification. None had experiences with the other two scales.

Table 1. Professional characteristics of raters

	Participant ($n = 31$)								
	Experienced with at least one BAHI skin reaction assessment scale ($n = 14$)				Inexperienced ($n = 17$)				
Profession	ENT clinician ($n = 6$)	ENT Resident ($n = 5$)	ENT Nurse Clinician ($n = 1$)	ENT Research ($n = 2$)	ENT Clinician ($n = 2$)	ENT Resident ($n = 1$)	ENT Research ($n = 4$)	Audiolo-gist ($n = 3$)	Other ($n = 7$)
Experience in profession	5 – 10 y ($n = 3$) 10–20 y ($n = 1$) 20–30 y ($n = 2$)	< 5 y ($n = 5$)	5–10 y ($n = 1$)	< 5 y ($n = 1$) 5–10 y ($n = 1$)	< 5 y ($n = 2$)	< 5 y ($n = 1$)	< 5 y ($n = 4$)	10–20 y ($n = 1$) 20–30 y ($n = 2$)	
Previously used scales	Holgers Classification				None				

Interrater Reliability

When considering all raters (regardless of experience), interrater reliability is moderate for the Holgers Classification and for the inflammation (I) and skin height (S) components of the IPS scale. A low to moderate reliability is observed for ratings that used the Tullamore scale (Table 2). Overall, the largest ICC point estimate is for the Holgers Classification, followed by the I and S displaying similar reliability assessments and the Tullamore classification showing the most variability amongst ratings.

Table 2. Interrater reliability for the scales used to assess post-operative BAHI skin reactions

Assessment scale for percutaneous BAHI	ICC (95% CI)		
	All raters ($n = 31$)	Experienced ($n = 14$)	Inexperienced ($n = 17$)
Holgers Classification	0.69 (0.52-0.87)	0.66 (0.48-0.85)	0.73 (0.56-0.89)
I (part of the IPS scale)	0.66 (0.49-0.85)	0.69 (0.51-0.87)	0.69 (0.52-0.87)
S (part of the IPS scale)	0.64 (0.47-0.84)	0.70 (0.52-0.88)	0.61 (0.42-0.82)
Tullamore Classification	0.60 (0.41-0.81)	0.75 (0.59-0.90)	0.49 (0.31-0.75)

Stratified analyses of participants with previous rating experience and those who had no prior experience (not familiar with BAHI skin reaction scales) was performed. In the case of inexperienced raters, the reliability of the scales follows a trend consistent with the results observed amongst all raters: the magnitude of the ICC point estimates is greatest for the Holgers Classification and significantly lower for the Tullamore Classification. Yet, the Tullamore Classification displays the most reliability when used by experienced raters while the Holgers Classification proved to be the least reliable with a low ICC (Table 2). The wide 95% confidence intervals of the ICC values compromise the precision of the results, because all include low ICC values (qualifying as questionable reliability) as well as high ICC values (qualifying as excellent reliability).

DISCUSSION

In this study, a comparison of the reliability for the grading of soft tissue reactions in percutaneous BAHIs was made among the Holgers Classification, IS scale and Tullamore Classification. Thirty-one participants completed the survey and rated pictures of BAHIs with

surrounding soft tissue according to the different grading systems. Overall as well as among inexperienced raters, the Holgers Classification demonstrates the least amount of variability amongst ratings. Nevertheless, considering among experienced raters, the Tullamore Classification showed the least variability.

Nowadays, the implantation of BAHIs is a safe procedure that could, under certain conditions, be performed under local anesthesia (4,21). The surgery can be performed in 15-20 minutes as a day procedure and is well tolerated by nearly all patients in our implant centers at the McGill University Health Center and the University Medical Center Utrecht. It is well-documented that the most common adverse event is skin reaction (17). Overall long-term skin reactions include mainly inflammation and soft tissue infections with a prevalence of 15–21% of all BAHI recipients (18,21). In contrast, a recent systematic review and meta-analysis investigating BAHI skin complications in the pediatric population shows a complication rate of 30% (22).

In the early post-operative stage, the skin around the abutment sometimes shows redness and tenderness. Rarely, we observe signs of granulation and secretions occurring several weeks after implantation, which result from the infiltrations by B cells, multinucleated cells and plasma cells following the surgical breach of the skin (13). Increased rates of skin hyperplasia around the implant occur in some susceptible individuals such as patients with known skin diseases (such as eczema, psoriasis, beaded red moss disease and hyperhidrosis) (14,16,17). Moreover. skin reactions could be caused by inappropriate surgical installation of the implant (i.e. direction of the implant not perpendicular to the skull or inadequate abutment length in relation to skin thickness). It has been demonstrated that prompt or inadequate wear of the sound processor could cause a loose base or friction between device and skin ultimately leading to skin reactions or implant

extrusion (14,16,17). Inadequate postoperative hygienic care increases the risk of implant site infections, which occurs more commonly in pediatric vs adult BAHI recipients (2,21).

Age-dependent anatomical differences can relate to a higher skin complication rate since children or elderly people commonly present with a softer and thinner skin compared to adults (23). the blood supply and microstructure are different in the pediatric skull bone compared to adults (18). Post-operatively, softer, more compliant bone may not tolerate the BAHI processor load, leading to excessive micromotion during the initial healing phase (19,20). This micromotion may affect the bacterial colonization and infection susceptibility at the skin level.

The importance of soft tissue reactions in patients with BAHIs demands an accurate grading scale. The Holgers Classification, as described by Holgers et al. (7), is the most wide-spread used grading system. This scale indicates no skin irritation as grade 0, mild redness as grade I, redness and moisture as grade II, granuloma formation as grade III and clear local skin infections as grade IV. Grades I and II are most often managed by abutment and skin cleaning and local antibiotics application while delaying or interrupting sound processor wear. Granulomas in grade III skin reactions are removed or treated with local caustic agents and similar treatment regimens to Grade I and II is applied. For the most severe grade IV soft tissue reactions, infections are controlled by surgical removal of inflammatory skin, local or systemic antibiotic treatment and the BAHI could be removed if treatment does not lead to satisfying outcomes or disease recurrence. Some studies define a Holgers grade II or higher as an adverse soft tissue reaction, because of the indication for (topical) treatment. (7).

The IPS scale was designed to assess long-term wound healing at the bone conduction site using both objective and patient reported measures of inflammation (skin integrity, erythema, edema and granulation tissue), pain, and skin height/numbness to prompt treatment decisions. The

IPS addresses the shortcomings of the Holgers Classification such as conflicting subjective responses, not considering long-term wound healing failures such as increased skin height and not encapsulating patient pain (7,12). Similar concerns were the reason for the development of the Tullamore Classification, which was presented during the International Congress on Bone Conduction Hearing and Related Technologies (2017, Nijmegen, the Netherlands) as a more suitable classification scale in 2017 (9).

A reliable classification system is essential to producing a standardized evaluation of the severity of post-operative skin reactions aimed at improving quality of the care and scientific investigation. More importantly, follow up of a postoperative complication is rarely performed by the same surgeon and often times another physician is involved (i.e. family physician, resident, colleague staff). To observe an optimal/reliable gradual improvement of the inflammatory site, it is important to be able to compare different timings of follow up. A suitable, clinical applicable classification is therefore indispensable. Currently, there is limited research evaluating the reliability of the BAHI skin reaction classification scales.

The limitations of this study should be considered. The confidence intervals of the ICC values preclude drawing conclusions about the strength of reliability. Although the 3D assessment of soft tissue reactions is done in a clinical setting, often with palpation to assess the status, this study used visual images. Participants with experience with skin classification scales were familiar with the Holgers scale and not the others, potentially leading to information bias. For the IPS scale, only the IS portion of the scale could be assessed.

CONCLUSION

The Holgers Classification seems to provide better reliability on reactions post BAHI surgery compared to the IPS and Tullamore, especially amongst inexperienced assessors.

Considering the added value of the IPS scale and its interrater reliability, this scale could also be used to assess BAHI skin reactions.

REFERENCES

1. Tjellström A, Lindström J, Hallén O, Albrektsson T, Brånemark PI. Osseointegrated titanium implants in the temporal bone. A clinical study on bone-anchored hearing aids. *Am J Otol* 1981;2:304–10.
2. Dun CA, Faber HT, de Wolf MJ, Mylanus EA, Cremers CW, Hol MK. Assessment of more than 1,000 implanted percutaneous bone conduction devices: Skin reactions and implant survival. *Otol Neurotol* 2012;33:192–8.
3. Den besten CA, Nelissen RC, Peer PG, et al. A retrospective cohort study on the influence of comorbidity on soft tissue reactions, revision surgery, and implant loss in bone-anchored hearing implants. *Otol Neurotol* 2015;36:812–8.
4. Bezdjian A, Smith RA, Thomeer HGXM, Willie BM, Daniel SJ. A Systematic Review on Factors Associated With Percutaneous Bone Anchored Hearing Implants Loss. *Otol Neurotol* 2018;39:897–906.
5. Gristina AG. Biomaterial-centered infection: microbial adhesion versus tissue integration. *Science* 1987;237:1588–95.
6. Mohamad S, Khan I, Hey SY, Hussein SS. A systematic review on skin complications of bone-anchored hearing aids in relation to surgical techniques. *Eur Arch Otorhinolaryngol* 2016;273:559–65.
7. Holgers KM, Tjellström A, Bjursten LM, Erlandsson BE. Soft tissue reactions around percutaneous implants: a clinical study of soft tissue conditions around skin-penetrating titanium implants for bone-anchored hearing aids. *Am J Otol*. 1988;9:56–9.

8. Kruyt IJ, Nelissen RC, Johansson ML, Mylanus EAM, Hol MKS. The IPS-scale: A new soft tissue assessment scale for percutaneous and transcutaneous implants for bone conduction devices. *Clinical Otolaryngology* 2017;42:1410–13.
9. Savage JH, Frawley T. Tullamore classification: Pbahs fixture site reaction reevaluation. *7th International Congress on Bone Conduction Hearing and Related Technologies,* Miami Beach, FL, USA. 2019.
10. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979;86:420–8.
11. Richman J, Makrides L, Prince B. Research methodology and applied statistics. *Physiother Can* 1980;32:253–7.
12. Wazen JJ, Young DL, Farrugia MC, et al. Successes and complications of the Baha system. *Otol Neurotol* 2008;29:1115–9.
13. Holgers KM. Characteristics of the inflammatory process around skin-penetrating titanium implants for aural rehabilitation. *Audiology* 2000;39:253–9.
14. van der Pouw CT, Mylanus EA, Cremers CW. Percutaneous implants in the temporal bone for securing a bone conductor: surgical methods and results. *Ann Otol Rhinol Laryngol* 1999;108:532–
15. Hobson JC, Roper AJ, Andrew R. Complications of bone-anchored hearing aid implantation. *J Laryngol Otol* 2010;124:132–6.
16. de Wolf MJ, Hol MK, Mylanus EA, Cremers CW. Bone-anchored hearing aid surgery in older adults: implant loss and skin reactions. *Ann Otol Rhinol Laryngol* 2009;118:525–31.
17. Fontaine N, Hemar P, Schultz P, Charpiot A, Debry C. BAHA implant: implantation technique and complications. *Eur Ann Otorhinolaryngol Head Neck Dis* 2014;131:69–74.

18. Drinias V, Granström G, Tjellström A. High age at the time of implant installation is correlated with increased loss of osseointegrated implants in the temporal bone. *Clin Implant Den Relat Res* 2007;9:94–9.

19. Willie BM, Yang X, Kelly NH, et al. Cancellous bone osseointegration is enhanced by in vivo loading. *Tissue Eng Part C Methods* 2010;16:1399–406.

20. Pilliar RM, Lee JM, Maniatopoulos C. Observations on the effect of movement on bone ingrowth into porous-surfaced implants. *Clin Orthop Relat Res* 1986;208:108–13.

21. Kiringoda R, Lustig LR. A meta-analysis of the complications associated with osseointegrated hearing aids. *Otol Neurotol* 2013;34:790–4.

22. Shapiro S, Ramadan J, Cassis A. BAHA Skin Complications in the Pediatric Population: Systematic Review With Meta-analysis. *Otol Neurotol* 2018;39:865–73.

23. McDermott AL, Sheehan P. Bone anchored hearing aids in children. *Curr Opin Otolaryngol Head Neck Surg* 2009;17:488–93.

24. Mulvihill D, Kumar R, Muzaffar J, et al. Inter-rater Reliability and Validity of Holgers Scores for the Assessment of Bone-anchored Hearing Implant Images. *Otol Neurotol* 2019;40:200–3.

25. Bezdjian A, Smith RA, Gabra N, et al. Experience with Minimally Invasive Ponto Surgery and Linear Incision Approach for Pediatric and Adult Bone Anchored Hearing Implants. Ann Otol Rhinol Laryngol 2020;129:380–87.

26. Verheij E, Bezdjian A, Grolman W, Thomeer HG. A Systematic Review on Complications of Tissue Preservation Surgical Techniques in Percutaneous Bone Conduction Hearing Devices. Otol Neurotol 2016;37:829–37.

LINKING STATEMENT

Intact epithelia constitute a barrier to protect the body from injury and intrusive mico-organisms. Once the barrier is perforated, protective inflammatory and immune responses are activated. This local response is referred to as wound-healing which involves a cascade of overlapping stages such as coagulation, inflammation, proliferation and remodeling (Singer & Clark 1999). The percutaneous abutment is the reason skin reactions when referring to post-operative bone anchored hearing implant skin tolerability. This abutment however is important to the design of the auditory systems. The next study discusses in a technical note and an algorithm the change of abutment.

4.5 Worn out screw technical note

Strategies for removing a worn-out Bone-Anchored Hearing Aid abutment screw

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Published in: Clin Otolaryngol. 2018 Apr;43(2):782-783.

INTRODUCTION

First developed by Tjellström over 35 years ago, bone-anchored hearing implants have been used effectively as a treatment for conductive or mixed hearing loss.[1] These devices have been implanted safely in adults and children with success rates of 90% or higher.[2] Nonetheless, bone-anchored hearing implants present certain adverse effects most commonly related to soft tissue reaction, implant stability, failure to osseointegrate or due to trauma. A less frequently discussed complication is difficulties presenting while changing the implant abutment a simple procedure that requires a specialist to remove the abutment screw using a company-supplied screwdriver in a clinical setting. Reasons for changing the abutment are often associated with skin overgrowth, irritation or infection that could sometimes be avoided with a longer abutment.[3] Occasionally, the abutment screw can be worn-out over time making it impossible to grip and unscrew. Thus, this can present with practical difficulties in removing the abutment from the fixture. To our knowledge, there has been only two reports describing similar incidents.[4, 5]

A patient with skin overgrowth at the abutment site presented at our clinic. We were confronted with the challenge of removing an abutment with a damaged screw. In an attempt to remove the abutment non-invasively, we opted for various techniques and used several instruments. Based on our clinical experience, we assessed several techniques to remove an abutment screw in a laboratory setting and reported a stepwise strategy, which aid specialists when encountering similar cases.

TECHNICAL DESCRIPTION

A stepwise strategy for removing a worn-out abutment screw is summarised in Figure 1. When performing these steps, stabilising the abutment should be performed with counter-torque wrench or forceps. First, we attempted to unscrew using the bone-anchored hearing aid set

screwdriver applying increasing pressure in an attempt to create grip to the blunt screw head (Step 1). Ferguson and MacAndie (2016) encountered a similar case that was successfully resolved by placing a surgical glove between the screwdriver and the abutment screw in order to create traction.[3] We attempted to replicate the following using a surgical glove and then different rubber materials with various thickness and texture (Step 2). Then, a specialised plier (Step 3) that could externally hold and turn small screws can be used. Unscrewing an abutment screw by gripping the external screw head with long nose pliers could be done. Nonetheless, the narrow space between the screw and the abutment head could present a challenge. Then, using an otology driller with a 1-mm diamond burr, two opposite-sided grooves of the screw cup can be created (Step 4a). This procedure can be performed in an outpatient treatment room; however, if the patient is in distress or very young, performing the drilling in the operating room is recommended. Continuous irrigation is required to remove metal debris, cool the screw and allow visualisation. During the procedure, the abutment should be stabilized with forceps. The drilling should be performed parallel to the axis of the screw not to destabilize the implant. Similar to a previous report, we recommend creating deep grooves as close to the base of the abutment as possible to avoid shearing forces from splitting the formed flanges on the abutment.4 Drilling the titanium screw head should be performed using a low RPM (4000 RPM) to lessen trauma. Continuous irrigation is recommended when drilling to remove metal debris and cooling the screw. Drilling in intervals is encouraged to allow cooling of the abutment. Once the grooves are made, a screwdriver of appropriate size can be used to unscrew the abutment from the fixture (Step 4b). The final strategy to remove a blunt abutment screw head would be to drill off the screw head completely (Step 5). Similarly at Step 4a, irrigation and drilling intervals are recommended. Once the screw is freed, a plier could be used to unscrew the bottom part of the topless screw.

1. Custom made screwdriver

2. Custom made screwdriver and rubber

3. Long nose plier

4a. Drilling two sides of the abutment screw while stabilizing the abutment and continuously irrigating

4b. Using a straight screwdriver while stabilizing the abutment

5. After drilling off the screw head

Figure 1. Management algorithm for removing a worn-out abutment screw

DISCUSSION

Bone-anchored hearing implants provide significant benefits in terms of overall quality of life. However, postoperative complications are not uncommon. While most complications reported in the literature are skin-related (ie overgrowth, inflammation, infection, granulation formation, irritation), other adverse events include failure of osseointegration, pain, trauma, headache, social burdens or lack of benefit. These complications can lead to explantation. Skin-related

complications can often be prevented by improved surgical techniques with tissue preservation and good hygiene instructions.[2,6] Otolaryngologist can also opt for a longer abutment to resolve skin-related complications.[3] Regular follow-up visits are essential to ensure the stability of the implant and status of the skin around the area and the abutment screw.

A less commonly described problem with these devices is related to mechanical failures such as the presence of a worn-out screw preventing abutment change. Strategies in preventing a screw from wearing out include good hygiene around the abutment area and of the screw. This includes removing dust and dirt from the head tightening (or loosening) the abutment. One should always use a counter-torque wrench to fixate the implant in place. Tightening using excessive force may cause damage to the titanium screw head.

With the increasing number of bone conduction hearing device implantations, defected, damaged or eroded abutment screws could be encountered in otolaryngology clinics. Based on our clinical experience, we created a stepwise strategy upon evaluating non-invasive techniques in a laboratory setting (Figure 1).

Our proposed methods can be performed in the outpatient setting at least up to the step where there is a need to drill the screw. It is important to note that the stability of the implant can be compromised when attempting to remove the screw, particularly when involving drilling (Steps 4-5). This should be evaluated prior to replacing the abutment.

REFERENCES

1. Tjellström A, Lindström J, Hallén O, Albrektsson T, Brånemark PI. Osseointegrated titanium implants in the temporal bone. A clinical study on bone-anchored hearing aids. Am J Otol. 1981; 2: 304- 310.

2. Dun CA, Faber HT, de Wolf MJ, Mylanus EA, Cremers CW, Hol MK. Assessment of more than 1,000 implanted percutaneous bone conduction devices: skin reactions and implant survival. Otol Neurotol. 2012; 33: 192- 198.

3. Monksfield P, Ho EC, Reid A, Proops D. Experience with the longer (8.5 mm) abutment for Bone-Anchored Hearing Aid. Otol Neurotol. 2009; 30: 274- 276.

4. Ferguson L, MacAndie C. From the bathroom to the bone-anchored hearing aid: an idea on how to remove a stripped abutment screw from a bone-anchored hearing aid. Clin Otolaryngol. 2016; 41: 620- 621.

5. Joshi A, Gray R, Mahendran S. A novel method to remove worn-out abutment from fixture of bone-anchored hearing aid (BAHA). Otolaryngol Head Neck Surg. 2006; 135: 631- 632.

6. Verheij E, Bezdjian A, Grolman W, Thomeer HG. A systematic review on complications of tissue preservation surgical techniques in percutaneous bone conduction hearing devices. Otol Neurotol. 2016; 37: 829- 837.

LINKING STATEMENT

The percutaneous nature of the bone anchored hearing implant is associated with skin reactions due to its skin penetrating abutment. Transcutaneous systems have recently emerged to offer an improved aesthetic appearance, require little care and have a low risk of soft-tissue reactions and fixture loss.

Chapter 5

Exploring transcutaneous systems

Audiologic and Peri-operative Outcomes of the Sophono™ Transcutaneous Bone Conduction Device: A Systematic Review

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Published in: Int J Pediatr Otorhinolaryngol. 2017 Oct;101:196-203.

ABSTRACT

Objective: To delineate the auditory functional improvement and peri-operative outcomes of the Sophono^{TM} transcutaneous bone conduction device.

Methods: Eligible articles presenting patients implanted with the Sophono^{TM} were identified through a comprehensive search of PubMed and Embase electronic databases. All relevant articles were reviewed to justify inclusion independently by 2 authors. Studies that successfully passed critical appraisal for directness of evidence and risk of bias were included.

Results: From a total of 125 articles, 8 studies encompassing 86 patients using 99 implants were selected. Most patients (79.1%) were children. Ear atresia (67.5%) was the most frequently reported indication for Sophono^{TM} implantation. Overall pure tone average auditory improvement was 31.10 (± 8.29) decibel. During a mean follow-up time of 12.48 months, 25 patients (29%) presented with post-operative complications from which 3 were deemed as serious implant-related adverse events (3.5%).

Conclusions: The Sophono^{TM} transcutaneous bone conduction device shows promising functional improvement, no intra-operative complications and minor post-operative skin related complications. If suitable, the device could be a proposed solution for the rehabilitation of hearing in children meeting eligibility criteria. A wearing schedule must be implemented in order to reduce magnet-related skin complications.

1. INTRODUCTION

Transcutaneous bone conduction hearing devices (BCHDs) are abutment-free implants that utilize the natural bone transmission as a pathway for sound to travel to the inner ear, bypassing the external auditory canal and middle ear. Transcutaneous BCHDs create vibrations through an intact skin (passive; i.e. Sophono^{TM}) or through the skull (active; i.e. Bonebridge^{TM}) to be sensed by the cochlea. These transcutaneous systems offer an improved aesthetic appearance, require little care and have a low risk of soft-tissue reactions and fixture loss [1,2].

The Sophono^{TM} transcutaneous BCHD was first developed in 2006 under the name Otomag System and, since 2010, produced by Sophono Inc. (Boulder, Colorado, USA) [3]. Currently, Sophono^{TM} implants are available in 42 countries and have been implanted in more than 4,000 patients [4]. The device is intended for children 5 years and older, presenting with conductive or mixed hearing loss or unilateral severe to profound sensorineural hearing loss that cannot be aided through conventional air conduction hearing aids (i.e. due to ear deformities) [4]. In case of single-sided deafness, the "hearing" ear should have normal hearing (≤ 20 dB) [5]. The transcutaneous passive BCHD is stimulated by an external mechanical transducer held by a magnetic retention system comprised of a titanium implant with 2 internal magnets fixated in the temporal bone. The external component includes a digital sound processor (Alpha 1 or the new generation Alpha 2) and a magnetic acrylic baseplate.

Although transcutaneous BCHDs like the Sophono^{TM} offer appealing benefits, hearing outcomes are suspected to underperform when compared to percutaneous BCHDs due to the dampening of sound due to sound transmission via the skin [6,7]. Prior to initiating a trial with this transcutaneous system in our paediatric clinics, we systematically reviewed published papers

presenting Sophono™ implanted patients to delineate the device's functional improvement and peri-operative outcomes.

2. METHODS

2.1. Search strategy

A literature review was conducted to identify the auditory and post-operative outcomes of the Sophono™ transcutaneous BCHD. Eligible articles published between 1975 and August 2016 were identified through a comprehensive search in PubMed and Embase electronic databases. The search strategy included medical subject headings, sub-headings, and text words such as "transcutaneous", "bone conduction", "Sophono", "Otomag", "bone conducting implant" and "bone conducting device". Cross-reference checking was conducted to retrieve studies not identified by in the initial search strategy. This review was conducted in concordance with PRISMA guidelines [8].

2.2. Study selection

Two authors (A.B., H.B.) screened the title and abstracts of articles retrieved by the electronic search concordant with the criteria for study eligibility. Articles presenting cases of hearing impaired pediatric and/or adult patients implanted with the Sophono™ transcutaneous BCHD were selected. Case reports or studies reporting less than 5 Sophono™ implanted patients were excluded. Non-human studies and articles presenting other types of bone conduction systems were excluded. Letters, commentaries, literature reviews and abstracts were not eligible for evaluation. No language restrictions were applied. When the same data were presented in more than one publication, the most recent was used for data extraction. Articles failing to clearly state which device was implanted were excluded. Studies describing patients without audiology

evaluation were excluded. All divergence among reviewers (A.B., H.B.) was resolved by discussion then consensus.

2.3. Quality assessment

All eligible articles underwent critical appraisal for directness of evidence (DoE) and risk of bias (RoB) performed by 2 authors (A.B., H.B.) using predefined criteria (Table 1a, 1b). DoE was assessed using 6 criteria: indication for surgery (clearly reported diagnosis), demographic data (including age at surgery, gender, implant laterality), description of surgical technique, complications, audiologic improvement (in decibel (dB)) and follow-up time (in months). RoB was assessed using 5 criteria: loss to follow-up, standardization of treatment, standardization of complication (according to Holgers classification) [9], missing data and standardization of audiologic tests (audiologic performance assessed according to a protocol and by an individual other than the surgeon). The DoE assessment was scored as high in articles where positive scores were attained on 5 or 6 criteria, as moderate in articles with positive scores on 3 or 4 criteria, and as low in articles with positive scores on less than 3 criteria (Table 1a, 1b).

The RoB assessment was scored as low in articles where positive scores were attained on 3 or more criteria, as moderate in articles with positive scores on less than 3 but more than 2 criteria, and as high in articles with positive scores on less than 2 criteria. Articles scoring high (H) for directness of evidence and low (L) or moderate (M) for risk of bias were included for data extraction (Table 1a).

2.4. Data extraction

The number of patients and Sophono^{TM} implants per study were extracted. Extracted data also included demographic population information such as gender, age at implantation and a mean follow-up time per study. Clinical outcomes included indication for surgery and intra-operative as

well as post-operative complications. Adverse events were deemed serious if surgical intervention was required or if healing took longer than one month. Functional improvements were evaluated by auditory gain: the difference between aided and unaided hearing thresholds (in dB).

3. RESULTS

3.1. Search results and critical appraisal

The study selection process is illustrated in Figure 1. A total of 125 articles were identified by the electronic databases. Following selection based on titles and abstracts, 35 articles were chosen for full text review. Following cross-reference checking then full text review, 13 articles were selected for critical appraisal based on DoE and RoB (Fig. 1). Critical appraisal resulted in the exclusion of 5 studies (Table 1a – marked in grey) [10-13]. Data was extracted from 8 articles that successfully passed critical appraisal (Table 1a – marked in white) [5,6,14-18].

Figure 1. Flow chart demonstration study selection

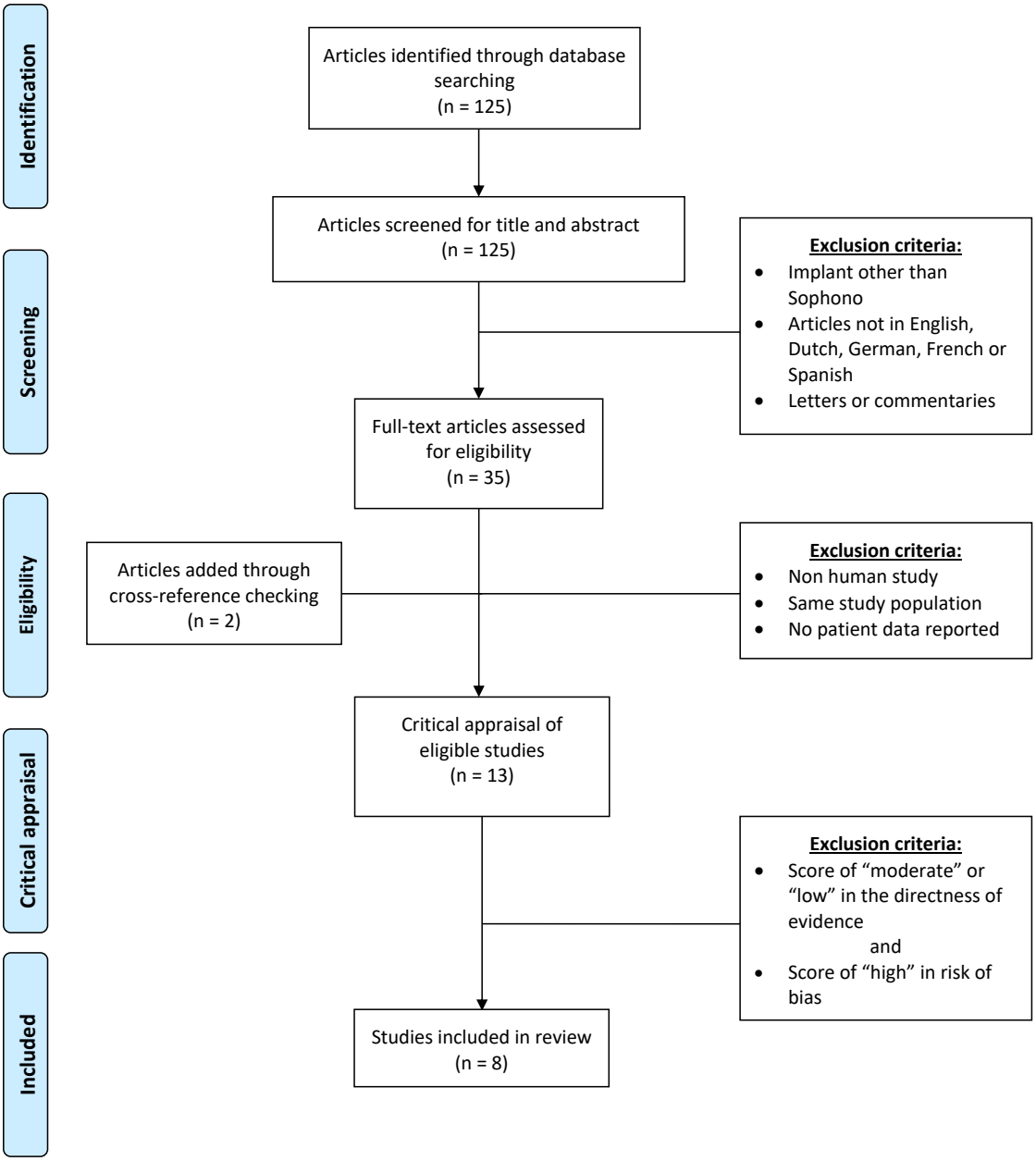

Table 1a. Critical appraisal of selected studies reporting on patients implanted with Sophono

		Directness of evidence (DoE)								Risk of bias (RoB)					
Authors	**Publication year**	**Study design**	**Indication for surgery**	**Demographic data**	**Description of surgical technique**	**Outcome measure (complications)**	**Outcome measure (auditory performance)**	**Follow-up**	**DoE score**	**Loss to follow-up**	**Standardization of treatment**	**Standardization of complication outcome**	**Standardization of audiologic tests**	**Missing data**	**RoB score**
Seigert *et al.* (5)	2013	RCS	●	◑	●	●	●	◑	**H**	●	○	○	●	◑	**M**
Hol *et al.* (6)	2013	RCS	●	●	●	●	●	◑	**H**	●	●	●	●	◑	**L**
O'Niel *et al.* (14)	2014	RCS	●	●	●	●	◑	◑	**H**	●	●	○	◑	◑	**L**
Marsella *et al.* (15)	2014	RCS	●	●	●	●	◑	○	**H**	●	○	○	●	●	**L**
Magliulo *et al.* (16)	2014	RCS	●	●	●	●	●	○	**H**	●	○	○	◑	●	**M**
Baker *et al.* (17)	2015	RCS	●	◑	●	●	●	●	**H**	●	●	○	◑	●	**L**
Denoyelle *et al.* (18)	2015	PCS	●	●	●	●	●	●	**H**	●	○	○	◑	●	**M**
Shin *et al.* (30)	2016	RCS	●	●	●	●	●	◑	**H**	●	●	○	◑	●	**L**
Powell *et al.* (10)	2015	CSCS	●	◑	○	○	◑	◑	**L**	◑	○	○	◑	◑	**H**
Sylvester *et al.* (11)	2013	RCS	●	◑	●	●	●	○	**M**	○	○	○	◑	○	**H**
Escorihuela-Garcia *et al.* (12)	2014	RCS	●	◑	○	●	●	◑	**M**	○	○	○	○	○	**H**
Leterme *et al.* (13)	2015	PCR	●	○	●	●	○	●	**M**	●	○	○	○	○	**H**
Bernardeschi *et al.* (31)	2016	RCS	●	●	○	○	●	○	**M**	●	○	○	◑	●	**H**

Table 1b. Assessment per item for critical appraisal of selected studies

	Grading (● = 1 point, ◑ = 0.5 point, ○ = 0 point)
Directness of Evidence (DoE)	
Study design	CSCS, cross sectional cohort study PCR, Prospective crossover study PCS, prospective case series RCS, retrospective case series
Indication for surgery *diagnosis*	clearly reported, ● not clearly reported, ○
Demographic data *age at surgery, gender, implant laterality*	complete, ● incomplete, ◑ not reported, ○
Description of surgical technique	clearly reported, ● not clearly reported, ○
Outcome measures on complications *specific occurrences of adverse events*	clearly reported, ● not clearly reported, ○
Outcome measures audiologic improvement	reported per patient, ● not individually reported (means), ◑ no audiologic test reported, ○
Follow-up *duration of follow-up for all tested individuals*	> 1 years, ● < 1 year, ◑ not reported, ○
Overall DoE score	Low, < 3 points, Moderate, between 3 - 4,5 points High, 5 points or <
Risk of Bias (RoB)	
Loss to follow-up	≤ 10%, ● > 10%, ◑ not reported, ○
Standardization of treatment *all included patients underwent the same treatment*	clearly reported, ● not clearly reported, ○
Standardization of complication *skin related complications according to Holgers classification*	clearly reported, ● not clearly reported, ○
Standardization of auditory tests *according to a protocol assessed by an individual other than surgeon*	clearly reported, ● reported however not standardized, ◑ not clearly reported, ○
Missing data	no missing data or missing data mentioned/quantified and method of handling described, ● missing data mentioned in study but method of handling not described, ◑ missing data not reported, ○
RoB score	High, <2 points Moderate, between 2-3,5 points Low, 3 points or >

3.2. Patient characteristics

Patients' characteristics from the included articles are presented in Table 2a and summarized in Table 2b. A total of 86 patients using 99 implants were included. The majority of included patients (68/86; 79.1%) were paediatric patients (< 18 years old) (total mean age: 17.18 years; range: 5 – 71 yrs). When reported, the gender distribution of implanted patients was equal (male: n = 33; female n = 33). Ear atresia was the most frequent indication (67.5%) for Sophono^{TM} implantation. One study included 10 patients (13%) who underwent subtotal petrosectomy and received a Sophono^{TM} implant [16]. Other indications for surgery included single sided sensorineural hearing loss (7.0%), cholesteatoma (3.5%) and presenting with a syndrome associated with conductive hearing loss (3.5%).

Table 2a. Sophono implanted patients' characteristics in selected studies

Study	Number of patients	Number of implants	Gender	Age at implantation in years [range]	Etiology (number of patients)
Siegert & Kanderske (5)	20	28	N/A	16 [6-50]	bil CHL from EA (11), CHL from EA (9)
Hol *et al.* (6)	6	6	4M, 2F	7.3 [5 - 11]	CHL from EA (5), OCA (1)
O'Neil *et al.* (14)	10	14	3M, 7F	9 [3.8 - 17.2]	CHL from EA (5), bil CHL from EA (2), ossicular fixation + cholesteatoma (1), bil CHL from cholesteatoma + EAC stenosis (1), bil cholesteatoma (1)
Marsella *et al.* (15)	6	6	3M, 3F	10.7 [5-17]	bil CHL from EA (2), from syndromic disease (3), mixed HL (1)
Magliulo *et al.* (16)	10	10	3M, 7F	47.8 [16 - 67]	Subtotal petrosectomy (10)
Baker *et al.* (17)	10	11	8M, 2F	10.7 [5 - 16]	SNHL (5), CHL from EA (3), CHL from COM (1), bil CHL post mastoidectomy (1)
Denoyelle *et al.* (18)	15	15	8M, 7F	8.1 [5.1 - 10.8]	CHL from EA (15)
Shin *et al.* (29)	9	9	4M, 5F	28.1 [5 - 71]	bil CHL from EA (5), from EA (1), SSD (2), COM (1)

Table 2b. Summary of outcomes of patients implanted with the Sophono transcutaneous implant

	Included, n (%)
Number of patients	86
Number of implants	99
Age at procedure	
Mean	17.18 y
Range	[5 - 71] y
Peadiatric patients, n	68 (79.1)
Gender, n	
Male	33 (50)
Female	33 (50)
Not reported	20
Etiology of hearing loss, n	
CHL from unilateral ear atresia	38 (44.2)
CHL from bilateral ear atresia	20 (23.3)
Unilateral subtotal petrosectomy	10 (11.6)
SNHL	6,0 (7.0)
Bilateral CHL from cholesteatoma	3.0 (3.5)
CHL from syndromic disease	3.0 (3.5)
Bilateral CHL post mastoidectomy	1.0 (1.2)
OCA	1.0 (1.2)
CHL post COM	1.0 (1.2)
Mixed HL	1.0 (1.2)
Unknown	1.0 (1.2)
Unaided audiologic outcomes	
PTA (Mean ± SD)	62.70 ± 9,31 dB
SRT (Mean ± SD)	66.90 ± 6.81 dB
Aided audiologic outcomes	
PTA (Mean ± SD)	31.60 ± 7.27 dB
SRT (Mean ± SD)	33.34 ± 4.74 dB
Auditory gain	
PTA (Mean ± SD)	31.10 ± 8.29 dB
SRT (Mean ± SD)	33.56 ± 5.64 dB
Complications, n	
Infection	6
Pain or tingling	5
Pressure discomfort	4
Erythema + pain	3
Erythema	3
Erythema + ulcer	2
Pressure necrosis	1
Headache	1
Follow-up time	
Mean	12.48 m
Range	[0.2 - 46.6] m

3.3. Auditory functional improvement

All studies included unaided and aided pure tone average (PTA) audiology outcomes. Included studies reported on average an unaided PTA of 62.70 (± 9.31) dB and an aided PTA of 31.60 (± 7.27) dB (Table 2b). Thus, PTA auditory gain in 86 patients implanted with the Sophono^{TM} transcutaneous device was 31.10 (± 8.29) dB. Five out of 8 studies reported unaided and aided sound reception thresholds (SRT), however only 4 of them (including 41 patients) were pooled because 1 study reported percentages instead of raw dB scores [5]. SRT scores resulted in a mean unaided score of 66.90 (± 6.81) dB and 33.34 (± 4.74) dB for aided SRT. A mean SRT gain of 33.56 (± 5.64) dB was found.

3.4. *Complications*

Mean post-operative follow-up time for Sophono^{TM} implanted patients was 12.48 months [0.2 – 46.6 months]. No intra-operative complications were reported. 29% of Sophono^{TM} implanted patients presented with post-operative complications. However, only 3 patients had serious adverse events (3.5% of all included patients).

Of the serious adverse events, one patient experienced skin breakdown requiring oral and local antibiotic treatment [14]. Surgical revision was required to improve implant seating, widen the wells and place a protective layer over the implant to prevent further skin breakdown. Another patient from the same study experienced skin breakdown and was treated with local antibiotics. However, the skin of the patient was already thinned due to a previous percutaneous device placement. Following ulceration healing, continued irritation and scabbing remained. Complete healing required 8 months [14]. The final patient developing a serious adverse event experienced post-operative severe headache. Subsequently, explantation was performed upon patient's request [17].

There were 21 patients (24.4%) who displayed minor implant-related skin complications. These included moderate to severe pain in 8 patients (9.3% of all included patients), pressure necrosis or discomfort was reported in 5 patients (5.8%), wound infection that resolved with antibiotics in 4 patients (4.7%), three of whom also had skin erythema (3.5%), isolated skin erythema in 3 patients (3.5%) and skin erythema with ulcer in 2 patients (2.3%). Two cases required surgical intervention [14,17].

4. DISCUSSION

4.1 *Summary of main results*

Published papers presenting Sophono^{TM} implanted patients were systematically reviewed to delineate the device's functional audiologic improvement (1) and peri-operative outcomes (2). The present systematic review revealed: 1) a PTA auditory gain of 31.10 (± 8.29) dB in 86 patients and a mean SRT gain of 33.56 (± 5.64) dB and 2) no intra-operative complications and minor post-operative complications in 29% of the patients. Only 3 patients (3.5%) had serious adverse events. Implant loss did not occur unless explanted, as seen in one patient [17].

4.2 *Comparison with other reviews and other devices*

From an auditory perspective, transcutaneous BCHDs like the Sophono^{TM} are thought to be less effective in terms of auditory functional improvement due to the dampening of sound vibrations through the skin when compared to percutaneous devices that allow direct coupling via the osseointegrated abutment. Early comparative laboratory assessments of the percutaneous and transcutaneous devices revealed a loss of between 10 and 15 dB at 1,000 kHz for transcutaneous devices [7,19]. However, more recent studies revealed better aided thresholds using improved transcutaneous systems [20-22]. The current review revealed functional improvements that seem

comparable to previously described methods of hearing restoration by percutaneous devices [17,20]. The major advantage of transcutaneous systems is the intact skin that decreases the risk soft-tissue complications. Increased risk of soft-tissue complications such as fixture loss, skin reactions, and infection have been found in children using percutaneous BCHDs [23]. Especially in children, careful wound care and skin hygiene is required around the abutment area to prevent these adverse outcomes. A review article evaluating 85 pediatric percutaneous implants identified a 46% complication rate where fixture loss occurring from trauma or failure of osseointegration was found in 26% of children [24]. Skin reactions such as skin irritation, erythema, and infection were reported in 37% of the children and revision surgery was required in 42% of cases. Another study reported a 52% rate of mild skin reactions, with 19% of patients requiring abutment replacement and 3% requiring revision surgery [25]. A review article compiling data from 8 studies reported a skin complication rate ranging from 2.4% to 44% of cases, revision surgery occurring in 7.5% to 25.9% of cases, and fixture loss in 5.3% to 40% of cases [26]. Only 1 patient (1.2%) included in the current review experienced skin breakdown [14] and needed revision surgery, compared to 3% to 25.9% requiring revision surgery in percutaneous BCHD studies [25,26]. However, recent research has described new surgical approaches for percutaneous BCHDs that successfully shorten operative time, have less implant failures, and reduce infection and soft-tissue reaction rates [27,28,29].

In order to reduce complications post Sophono^{TM} implantation, authors successfully implemented a device-wearing schedule starting with the lowest magnetic strength at initial fitting, followed by a gradual increase in strength and duration of wearing [14,18]. Transcutaneous systems have their clear benefits to the paediatric population because they do not required no daily skin maintenance, fixture extrusion due to trauma does not occur, shorter time to processor use is

recommended and lower revision surgery rates as well as skin complications are reported. Nonetheless, the surgical procedure is more invasive in nature than recent percutaneous implants [27]. Moreover, it is not uncommon for pediatric patients requiring BCHDs to have other co-morbidities such as neurological conditions and thus, may required one or repeated magnetic resonance imaging (MRI). Consequently, the magnetic components in the Sophono™ may have practical implications in patients requiring MRI. The FDA has cleared the Sophono™ Alpha System for use in MRI scanners with both 1.5-T and 3-T magnetic fields. However, the important distortion on MRI images, risks of demagnetization and risk of adverse effects on the device's output cannot be ignored. Clinicians should be mindful of this when considering these implant choices.

4.3. *Quality of Evidence and Potential Biases in Review*

Since the Sophono™ device is fairly novel, the limited number of implanted patients should be highlighted especially when making comparisons with other devices that have been used over the last two decades. More extensive comparative clinical studies are needed to adequately compare outcomes of various available bone conduction hearing devices.

4.4. *Implications for Clinical Practice and Recommendations*

Due to its apparent advantages and functional improvement reported in 86 patients, it appears that the Sophono™ transcutaneous device could be a proposed solution for the rehabilitation of hearing in children meeting eligibility criteria. There are still important challenges that should be considered when choosing transcutaneous BCHDs mostly related with reaching optimal auditory gain, invasive nature of surgical procedure, and magnetic resonance imaging compatibility. Therefore, the results of the present systematic review can be used in discussing

auditory rehabilitation options with families. If the SophonoTM device is elected, a wearing schedule can be implemented in order to reduce magnet-related skin complications.

5. CONCLUSION

The Sophono^{TM} transcutaneous BCHD shows satisfactory auditory functional improvement, no intra-operative issues and minor post-operative skin related complications. The device could be a proposed solution for hearing rehabilitation in children meeting eligibility criteria. A wearing schedule can be implemented in order to reduce magnet-related skin complications. Additional studies including larger study samples comparing outcomes and complications of different types of transcutaneous and percutaneous BCHDs are encouraged.

REFERENCES

1. Sprinzl G, Lenarz T, Ernst A, et al. First European multicenter results with a new transcutaneous bone conduction hearing implant system: short-term safety and efficacy. *Otol Neurotol* 2013;34:1076–83.
2. Barbara M, Perotti M, Gioia B, et al. Transcutaneous bone conduction hearing device: audiological and surgical aspects in a first series of patients with mixed hearing loss. *Acta Oto-laryngol* 2013;133:1058–64.
3. Sophono Inc. 2015 Medtronic completes acquisition of Sophono, Inc., bone conduction hearing implant technology; available at: http://www.sophono.com Accessed July 1, 2016.
4. Siegert R. Partially implantable bone conduction hearing aids without a percutaneous abutment (Otomag): technique and preliminary clinical results. *Adv Oto-rhino-laryng* 2011;71:41-6.
5. Seigert R, Kanderske J. A new semi-implantable transcutaneous bone conduction device: clinical, surgical, and audiologic outcomes in patients with congenital ear canal atresia. *Otol Neurotol* 2013;34:927-34.
6. Hol MK, Nelissen RC, Agterberg M, et al. Comparison between a new implantable transcutaneous bone conductor and percutaneous bone-conduction hearing implant. *Otol Neurotol* 2013;34:1071-5.
7. Håkansson B, Tjellström A, Carlsson P. Percutaneous vs. transcutaneous transducers for hearing by direct bone conduction. *Otolaryng Head Neck* 1990;102:339-44.
8. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006-12.

9. Holgers KM, Tjellström A, Bjursten LM, et al. Soft tissue reactions around percutaneous implants: a clinical study of soft tissue conditions around skin-penetrating titanium implants for bone-anchored hearing aids. *Am J Otol* 1988;9:56-9.
10. Powell HR, Rolfe AM, Birman CS. A comparative study of audiologic outcomes for two transcutaneous bone-anchored hearing devices. *Otol Neurotol* 2015;36:1525-31.
11. Sylvester DC, Gardner R, Reilly PG, et al. Audiologic and surgical outcomes of a novel, nonpercutaneous, bone conducting hearing implant. *Otol Neurotol* 2013;34:922-6.
12. Escorihuela-García V, Llópez-Carratalá I, Pitrach-Ribas I, et al. Initial experience with the Sophono Alpha 1 osseointegrated implant. *Acta Otorrinolaringo Esp* 2014;65:361-4.
13. Leterme G, Bernardeschi D, Bensemman A, et al. Contralateral routing of signal hearing aid versus transcutaneous bone conduction in single-sided deafness. *Audiol Neuro-otol* 2015;20:251-60.
14. O'neil MB, Runge CL, Friedland DR, et al. Patient outcomes in magnet-based implantable auditory assist devices. *JAMA Otolaryngol Head Neck Surg* 2014;140(6);513-20.
15. Marsella P, Scorpecci A, Vallarino MV, et al. Sophono in pediatric patients: the experience of an Italian tertiary care center. *Otolaryng Head Neck* 2014;15:328-32.
16. Magluilo G, Turchetta R, Iannella G, et al. Sophono Alpha System and subtotal petrosectomy with external auditory canal blind sac closure. *Eur Arch Oto-rhino-l* 2015;272:2183-90.
17. Baker S, Centric A, Chennupati SK. Innovation in abutment-free bone-anchored hearing devices in children: Updated results and experience. *Int J Pediatr Otorhi* 2015;79:1667-72.

18. Denoyelle F, Coudert C, Thierry B, et al. Hearing rehabilitation with the closed skin bone-anchored implant Sophono Alpha1: Results of a prospective study in 15 children with ear atresia. *Int J Pediatr Otorhi* 2015;79:382-7.

19. Håkansson B, Tjellstrom A, Rosenhall U. Hearing thresholds with direct bone conduction versus conventional bone conduction. *Scand Audiol* 1984;13:3-13.

20. Reinfeldt S, Håkansson B, Taghavi H, et al. New developments in bone-conduction hearing implants: a review. *Med Devices (Auckl)* 2015;16:79-93.

21. Reinfeldt S, Håkansson B, Taghavi H, et al. The bone conduction implant: Clinical results of the first six patients. *Int J Audiol* 2015;54:408-16.

22. Håkansson B, Eeg-Olofsson M, Reinfeldt S, et al. Percutaneous versus transcutaneous bone conduction implant system: a feasibility study on a cadaver head. *Otol Neurotol* 2008;29:1132-9.

23. Doshi J, Sheehan P, McDermott AL. Bone anchored hearing aids in childen: An update. *Int J Pediatr Otorhinolaryngol* 2012;76(5):618-622.

24. Stewart CM, Clark JH, Niparko JK. Bone-anchored devices in single-sided deafness. *Adv Otorhinolaryngol* 2011;71:92-102.

25. Nelissen RC, Agterberg MJ, Hol MK, et al. Three-year experience with the Sophono in children with congenital conductive unilateral hearing loss: tolerability, audiometry, and sound localization compared to a bone-anchored hearing aid. *Eur Arch Oto-Rhino-L* 2016;273(10):3149-56.

26. de Wolf MJF, Hol MKS, Huygen PLM, Mylanus EAM, Cremers CW. Nijmegen results with application of a bone-anchored hearing aid in children: simplified surgical technique. *Ann Otol Rhinol Laryngol* 2008;117(11):805-814.

27. Johansson ML, Stokroos RJ, Banga R, et al. Short-term results from seventy-six patients receiving a bone-anchored hearing implant installed with a novel minimally invasive surgery technique. *Clin Otolaryngol* 2017 [epub ahead of print].
28. Hultcrantz M. Outcome of the bone-anchored hearing aid procedure without skin thinning: a prospective clinical trial. *Otol Neurotol* 2011;32(7):1134-9.
29. Verheij E, Bezdjian A, Grolman W, Thomeer HG. A systematic review on complications of tissue preservation surgical techniques in percutaneous bone conduction hearing devices. *Otol Neurotol* 2016;37(7):829-37.
30. Shin JW, Kim SH, Choi JY, et al. Surgical and audiologic comparison between sophono and bone-anchored hearing aids implantation. *Clin Exp Otorhinolar* 2016;9(1):21-4.
31. Bernardeschi D, Russo FY, Nguyen Y, et al. Audiological Results and Quality of Life of Sophono Alpha 2 Transcutaneous Bone-Anchored Implant Users in Single-Sided Deafness. *Audiol Neuro-Otol* 2016;21(3):158-164.

LINKING STATEMENT

The innovative transcutaneous systems show satisfactory auditory functional improvement, no intra-operative issues and minor post-operative skin related complications. The device could be a proposed solution for hearing rehabilitation particularly in children or those who do not want a percutaneous implant screw.

The next paper discusses an important topic when evaluating auditory improvement of bone anchored hearing systems; functional gain.

How to quantify the 'auditory gain' of a bone-conduction device

Reply to the Editor

Aren Bezdjian, Hanneke Bruijnzeel, Sam J Daniel, Hans GXM Thomeer

Published in: Int J Pediatr Otorhinolaryngol. 2018 Jun;109:187.

How to quantify the 'auditory gain' of a bone-conduction device; comment to the systematic review by Bezdjian et al. (2017) by Prof. Ad Snik

Dear editor During the last decades, several new types of bone-conduction devices (BCDs) have been released for patients with conductive or mixed hearing loss. One of the latest innovations is the transcutaneous Sophono device (Medtronic; Jacksonville, Fl, USA) [1]. This device makes use of a transcutaneous magnetic coupling between the externally worn BCD and the skull. Recently, Bedzjian et al. published a systematic review on clinical results with this device [2]. Data regarding 'functional improvement' and peri-operative medical outcomes were reviewed. The 'functional improvement' or 'auditory gain', as introduced by the authors, was defined as the difference between aided and unaided soundfield thresholds. In sensorineural hearing loss, the 'auditory gain' (mostly referred to as 'functional gain') is a measure of the gain (amplification) provided by the device [3]. That is not the case for conductive or mixed hearing loss when using a BCD; BCDs directly stimulate the cochlea, bypassing the impaired middle ear and thus the air-bone gap. Owing to the definition of 'auditory gain', the width of that air-bone gap directly affects the 'auditory gain'. To illustrate this: in case of aural atresia, assuming a mean hearing loss of 70 dB HL and a mean 'auditory gain' of 30 dB, the aided thresholds are poor, 40 dB HL. In case of mild conductive hearing loss of 40 dB HL, e.g. owing to chronic otitis media, an 'auditory gain' of 30 dB implies near-normal hearing with the device. Obviously, the latter patient has more adequate amplification, although the 'auditory gain' is the same for either patient. As has been suggested before, it is more useful to analyse the aided thresholds in relation to the cochlear thresholds (boneconduction thresholds) [4]. The authors reported that the mean 'auditory gain', averaged over studies, was 31.6 dB. It was concluded that this was a satisfactory result, however, as indicated above, it only indicates that the BCDs did work but not how adequately they were

fitted. Furthermore, it is not appropriate to average the 'auditory gain' over studies with heterogeneous patient groups comprising patients with conductive hearing loss or mixed hearing loss or even single-sided deafness. Concerning patients with single-sided deafness, by definition, the 'auditory gain' is expected to be 0 when using a BCD as a CROS device [3]. It is suggested that the authors present the aided thresholds and the bone-conduction thresholds of the patients with conductive hearing loss and mixed hearing loss separately, to illustrate the real capacity of the Sophono device. At last, it should be noted that using aided thresholds to assess the gain of a device is not straightforward if non-linear amplification is applied. However, in this case, it seems to be justified as amplification was most probably linear, which is concluded from the fact that the reported 'auditory gain' derived from free-field tone thresholds (31.6 dB) was comparable to that derived from SRTs (the 'supra-threshold' speech reception thresholds; 33.6 dB).

References

[1] R. Siegert, J. Kanderske, A new semi-implantable transcutaneous bone conduction device: clinical, surgical, and audiologic outcomes in patients with congenital ear canal atresia, Otol. Neurotol. 34 (2013) 927–934.

[2] A. Bezdjian, H. Bruijnzeel, S.J. Daniel, W. Grolman, H.G.X.M. Thomeer, Preliminary audiologic and peri-operative outcomes of the Sophono™ transcutaneous bone conduction device: a systematic review, Int. J. Pediatr. Otorhinolaryngol. 101 (2017) 196–203.

[3] H. Dillon, Hearing Aids, Thieme Medical Publishers, Stuttgart, 2012.

[4] P.U. Carlsson, B.E. Håkansson, The bone-anchored hearing aid: reference quantities and functional gain, Ear Hear. 18 (1997) 34–41.

Response to “How to quantify the 'auditory gain' of a bone-conduction device; comment to the systematic review by Bezdjian et al.”

The authors would like to thank Prof. Ad Snik for his insightful comment following our recent publication. This published systematic review includes reported patient outcomes gathered from 8 articles. An insight on the operative and audiological impact of the investigated transcutaneous bone conduction device was sought out.

The quantification of auditory gain, as highlighted out by Prof. Snik, is challenging in patients aided by bone conduction hearing devices. Averaging auditory gain over studies with heterogeneous patient groups does not give an adequate overview of the devices auditory outcomes. This is particularly pertinent when evaluating audiological outcomes from patients with different types of hearing loss (i.e. conductive, mixed, single sided hearing loss). Amplification done by a bone conduction hearing device is most adequately analysed in relation to bone-conduction thresholds. The nature of our study, being a systematic review, summarises the available results of selected studies. Unfortunately, most included studies did not report bone conduction thresholds. It would be desirable to include these in future prospective study evaluating outcomes of bone conduction hearing implants.

In order to better the reported outcomes of included studies in our systematic review, a supplemental table was constructed. This table includes unaided and aided audiological evaluations and all available data reflecting on the benefit of the implantable device. It is important to note that even within study, there is heterogeneous patient populations in regard to different etiology and/or laterality of hearing loss of presented patient cohorts.

We believe that a most accurate representation of audiological benefits of bone conduction hearing device is best represented by a paradigm that compromises more than a comparison of

auditory and bone conduction thresholds alone. In our experience, patient reported questionnaires could provide important insights and compliment the evaluations done in the surgical and audiological setting.

Supplemental Table. Audiological and quality of life outcomes of Sophono^{TM} implanted patients in selected studies

Study	Unaided outcomes in dB (Mean ± SD)	Aided outcomes in dB (Mean ± SD)	Auditory improvement in dB (Mean ± SD)	Follow up time in months [range]
Siegert & Kanderske (2013)	PTA: 58.7 ± 8.2 SRT: 15.3% ± 22.9%	PTA: 29.7 ± 8.2 SRT: 76.8% ± 18.2%	PTA: 29 ± 8.2 SRT: 61.5% ± 20.55%	19.3 [0.2 - 46.6]
Hol *et al.* (2013)	PTA: 57.83 ± 4.07 PTA BC: 6.50 ± 4.51 SRT: 57.50 ± 13.33 WRS: 23 ± 46	PTA: 36.33 ± 3.93 SRT: 30 ± 2.76 WRS: 84.33 ± 10.39	PTA: 21.5 ± 4 SRT: 27.5 ± 11.86	10.68 [4.76 - 24.31]
O'Neil *et al.* (2014)	PTA: 60.3 ± 14.2	PTA: 20.2 ± 6.0	PTA: 40.1 ± 10.1	11.6 [4.5 - 24.0]
Marsella *et al.* (2014)	PTA: 65 ± 4.69 TIPI: 61.17 ± 18.34	PTA: 32.5 ± 5.47 TIPI: 91.67 ± 7.2 GCBI: + 38 ± 21.17	PTA: 32.5 ± 5.08 TIPI: 30.5 ± 12.77	N/A
Magliulo *et al.* (2014)	PTA: 71.86 ± 8.86 PTA BC: 28.87 ± 6.16 SRT: 72.1 ± 8.49 WRS: 3 ± 6.75	PTA: 42.09 ± 7.57 SRT: 38 ± 5.37 WRS: 87.1 ± 6.54	PTA: 29.77 ± 8.22 SRT: 34.1 ± 6.93 WRS: 84.1 ± 6.65	N/A
Baker *et al.* (2015)	PTA: 63.38 ± 12.81 SRT: 66.25 ± 18.47	PTA: 28.3 ± 10.31 SRT: 27.22 ± 12.02	PTA: 35.08 ± 11.56 SRT: 39.03 ± 15.25	14.62 [3.98 – 25.07]
Denoyelle *et al.* (2015)	PTA: 69.02 ± 9.31 SRT: 71.73 ± 9.20	PTA: 36.43 ± 4.61 SRT: 39 ± 5.86	PTA: 32.59 ± 6.96 SRT: 32.73 ± 7.53	19 [12 - 32]
Shin *et al.* (2016)	PTA: 54.5 ± 9.5 PTA BC: 22.75 ± 18.40	PTA: 29 ± 10.8	PTA: 25.5 ± 11.7	8.4 [4 - 12]

GCBI, Glasgow Children's Benefit Inventory (in gains); N/A, not available; PTA, pure tone average; PTA BC, mean bone conduction thresholds in dB at 0.5, 1, 2, and 4 kHz of the atretic side; SD, standard deviation; SRT, speech reception threshold; TIPI, Italian adaptation of the Northwestern University Children's Perception of Speech Instrument (in % of correct scores), WRS = word recognition score.

Chapter 6

Summary and conclusions

Implant stability with subsequent osseointegration is the primary factor leading to implant survival. The determinant of primary stability occurring at the moment of placement is the implant design, and the mechanical properties of the bone tissue permitting the anchorage at the bone-implant interface. The integrity of this interface is of great important when evaluating the success of the implantation, preventing implant extrusions, and determining the optimal time for processor coupling to the implant abutment. Implant extrusion can occur spontaneously even years after surgery. A systematic review compiling 51 articles where bone anchored hearing implant extrusion was reported and passed quality assessment, showed an extrusion rate of 7.3% [Paper 1]. This finding is the first of its kind, suggest that extrusions are more common than some reports had stated (Kiringoda et al., 2013; Larsson et al., 2015). Three hundred and one implant losses occurred out of 4,116 implants placed investigated in the review. Failed osseointegration was responsible for most implant losses (74.2%), followed by fixture trauma (25.7%). Most losses due to failed osseointegration occurred within 6 months of the implantation suggesting that an initial primary stability made possible by the implant placement was not accompanied by osseintegration. The study revealed that extrusions occurred more frequently in pediatric implant recipients. It is expected that traumatic events occur more frequently in this patient cohort, however, age-dependant bio-structural bone differences may also contribute to a superior extrusion rate in younger recipients. Pediatric skull bones contain air cells, and are softer and more compliant, thus, may not tolerate the processor load that causes micromotion during the initial healing phase (Pilliar et al., 1986; Willie et al., 2010). Thus, this could necessitate a longer osseointegration period and require delayed processor coupling protocols. In fact, when using the RFA to determine stability trends, we observe that [Paper II] osseointegration of the bone-implant interface takes longer than adults. Nonetheless, the interpretation of the RFA system derived ISQ score is under scrutiny.

The evaluation of the integrity of the bone-implant interface of bone anchored hearing implants is warranted as it could aid clinicians to decide the timing of loading of the sound processor, prevent implant extrusions, and monitor post-operative implantation success. The advent of a novel tool determining the stability of the anchorage is needed. Resonance frequency analysis was introduced by Meredith et al. to clinically test implant dental and orthopedic stability in a non-destructive manner (Meredith et al., 1998). The instrument measures the resulting resonance frequency (in Hz) and translates this into a more clinically useful implant stability quotient (ISQ) scale. The ISQ scales ranges from 1 to 100; the higher the ISQ, the more stable the implant. Measurements are conducted in 2 perpendicular directions resulting in two different ISQ values: ISQ high and ISQ low. The group that introduced the tool conducted a prospective cohort study where scores derived from 195 dental implants were correlated bone and implant related features (Sennery & Meredith, 2000). It was demonstrated that longer and wider implants had higher primary stability compared to shorter and narrower dental implants. However, this association was made evident when investigating secondary stability (osseointegration). The same statement was made for bone anchored hearing implants in a paper by Calon et al. (2018) highlighting that primary stability is influenced by abutment length, bone quality and degree of seating. Thus, there is a general consensus that the interpretation of absolute ISQ scores alone is not recommended. The individual trends in ISQ scores within a same individual should be analyzed in order to see how the scores progresses post-operatively (Nelissen et al., 2015). This methodology was implemented for all studies in this thesis that included the ISQ system for analysis [Papers II, III, VII].

Implant geometry (i.e. diameter, thread profile) and drilling protocol, as well as abutment length and status of skin surrounding the implant are factors that have shown to influence the RFA measurement (Calon et al., 2018; Kruyt et al., 2018). For these reasons, threshold shifts (difference from baseline within a patient) were gathered to display mean development of implant stability and to allow comparison of scores between pediatric and adult patients as they hold constant implant related influencing factors (Paper II). The clinical data looked at intra-operative ISQ scores and how they progressed at follow up visits in two cohorts of patients. The study allowed for the following conclusion: 1) for pediatric patients, a 6-week latency period prior to coupling the sound processor is warranted and 2) for adults, processor coupling could likely be performed as soon as skin around the abutment site has healed. The trends in early coupling of the sound processors is increasingly being sought out by clinicians worldwide. Data from the dental field shows that implants may be successfully loaded before osseointegration is complete as long as good primary stability is maintained (Gapski et al., 2003). Recent clinical data show successful adoption of early processor coupling protocols for osseointegrated auditory implants in pediatric and adult patients. Hogsbro et al. safely coupled the sound processor 1 week after surgery for adult patients with expected normal bone quality and no extrusion and conflicting condition (Hogsbro et al., 2017). These studies suggest that micromotions from the sound processor are negligible and do not affect osseointegration. Nonetheless, while these data are promising, further clinical and preclinical assessment is needed to understand what bone and patient specific factors influence the RFA measurement and its relationship with implant stability [Paper III].

In an attempt to delineate the structural and mechanical properties that influence the RFA system, the artificial and cadaveric skull bone analysis conducted in Paper II revealed several interesting findings. First, it is clear that stability scores were significantly lower in compromised

(osteoporotic) bone. Osteoporosis has been shown to be a risk factor for impaired healing and osseointegration (Goldhahn et al., 2008; Kim et al., 2001). Recent studies claim that patients with osteoporosis do not have a higher risk of early implant failure compared to non-osteoporotic patients suggesting that bone mineral density influences primary stability (Marquezan et al., 2012). Our study, in concordance to publications investigating dental implants, reveal that implant stability as assessed by the ISQ score of the RFA system seems to be influenced by bone density (Merheb et al., 2016). The lower stability scores in patient with osteoporosis reinforce recommendations that safe protocols and longer healing times could be recommended when treating when placing auditory implants in this patient population (Merheb et al., 2016).

The relationship between temporal skull bone thickness, a crucial factor in osseointegration and implant stability, and age has been well-established (Lynnerup 2005; Lillie 2015; Baker 2016; Tomlinson 2017). Clinical studies have demonstrated that cortical thickness is strongly correlated to an increase in primary stability as measured by the ISQ score (Merheb et al., 2017). The non-linear relationship between ISQ scores and age of donor was discovered in our laboratory assessments. The positive correlation between peak load and age of donor was a noteworthy finding for two reasons. First, cadaveric bone is not living bone, meaning that age-related dynamic bone-processes should not have an impact on BAHI stability post-implantation. Second, age-related skull bone properties have not been previously shown to offset the aforementioned non-linear relationship between temporal skull bone thickness and age. This is a key finding that also supports the conclusions of Paper II, due to the current paucity in knowledge regarding the effect of age as a factor in auditory implant stability.

Similarly, an investigation into the role of gender as a factor in bone quality and implant stability was conducted. Previous studies demonstrate a there are significant gender and temporal

skull differences (Lillie 2015; Lynnerup 2005). In the field of dental implants, previous studies have demonstrated a significant effect of gender on implant stability in the short-term (Andersson 2019; Guler 2013). In particular, dental implants have been shown to yield significantly higher ISQ scores in men directly after implantation and up to 4 weeks after implant placement. However, gender did not have an effect on long-term implant stability or survival in any of these studies. These studies had relatively long wait periods between measurements that are not translatable to the protocols in the auditory implant field.

Elderly hearing-impaired individuals may benefit from BAHIs if they meet eligibility criteria. As the aging process occurs, bone resorption exceeds bone formation, reducing bone mass, increasing bone fragility (Demontiero et al., 2012). There is also an accompanying age-related reduction in the bone formation response to mechanical loading that likely deleteriously affects healing around the implants (Razi et al., 2015). Owing to these factors, it would be beneficial to assess bone mass and quality in elderly patients before BAHI implantation. The cadaveric study attempted to do so but did not show effect of age on the force needed to displace the implant and the stability scores. This could be associate with the low sample size of cadaveric donors and the lack of young skull bones to allow adequate comparison.

The influence of the surgical approach to bone anchored hearing implantation is also evaluated in this thesis. A report comparing the two surgical approaches similar to the Paper VII of this thesis shows that ISQ was significantly influenced by the surgical technique (2.4 points lower in the MIPS group) (Calon et al., 2018). In contrast, our cohort and several reports in the field of dentistry show otherwise. In the dental field, flapless procedures demonstrated slightly higher ISQ values compared to the open methods (Katsoulis et al., 2012; Merheb et al., 2017). The MIPS cohort in our study (Paper VII) had consistently higher ISQ scores intra-operatively and at

every follow-up time point tested. The initial stability could be influenced by the MIPS punch technique that allows the surgery to be performed via a cannula. Thus, the intact skin could create a cuff of tissue around the implant positively influencing the stability. The thesis highlights the primary advantages of the novel MIPS approach: 1) shorter surgical duration and 2) more implantations performed using local anesthesia and sedation (Paper VII). It has been shown that implant losses are more common following the MIPS approach, however our retrospective cohort series showed the opposite as it had no extrusions in the MIPS cohort (Calon et al., 2018). The linear incision technique is still performed as it a main advantage over the MIPS or other approaches; more visibility during osteotomy and implant placement and less risk of thermal damage due to more access for irrigation (Sclar, 2007). Nonetheless, this approach has also seen enhancements, primarily that discussed in Paper V. Nowadays, most procedures occur in a single-stage procedure where placement of the fixture and abutment are implanted during the same surgical intervention. The standard surgical procedure included thinning of the skin around the implant. The rationale behind skin thinning is to assure tight contact between skin and bone tissue in order to avoid mobility and overgrowth of the skin surrounding the abutment and diminishing the risk of infections (Cass & Mudd, 2010). With the advent of longer abutments, the possibility to implant without soft tissue reduction while also maintaining adequate stability has been suggested (Hultcrantz, 2015). In a systematic review, Paper V showed that without skin thinning, less surgical trauma and a smaller risk of devascularization could occur leading to faster healing with less skin complications (Altuna et al., 2015; Hultcrantz 2015). The findings of the review found that complications following surgeries did not differ when the skin is thinned or preserved. Since its publication in 2016, the study has been cited 33 times, suggesting that the surgical approach is being widely opted.

In Papers II, V, VII, and VIII, skin tolerability, the most recurring adverse event seen in percutaneous bone conduction hearing systems were evaluated and discussed. In recent clinical series evaluating outcomes of percutaneous systems, a 23.9% complication rate was reported (i.e. adverse skin reactions or infections) (Hobson et al., 2010). During the initial phase of healing around a percutaneous implant, there is a bodily response involving several cell types and microorganisms (Grintina, 1987). The creation of a structural and functional barrier between the skin and the implant is created. A flow of bacterial invasion occurs resulting in an inflammatory response following the epithelial downgrowth and pocket formation (Holgers et al., 1995). As a result, granulation tissue, epidermal downgrowth and biofilm production is observed. In concordance with other reports, the thesis reveal that tissue reactions are influenced by surgery-related factors such as the surgical approach, implant type and location, abutment length and post-operative dressing, or by patient-related factors that influence wound healing, hygiene and self-care such as skin and skull thickness, and comorbidities (Papers III, V, VII, X) (Mohamad et al., 2016). Currently, most centers assess skin tolerability post-implantation using the Holgers Classification, which evaluates redness, swelling, moistness and/or granulation around the skin penetrating implant (Holgers et al., 1988). A reliable skin tolerability classification scale is important in the evaluation of post-operative reactions for delivery of appropriate care and continuity. Recently, new scales have emerged addressing perceived shortcomings of the commonly used Holgers Classification which were compared in an inter-rater variability study (Paper VIII). The rationale behind this study is that two observers could assign two different rating on a same reaction, hindering doubts about the validity of the scales. The Holgers Classification seems to provide better reliability on reactions post BAHI surgery compared to the two new scales, especially amongst inexperienced assessors. However, variability still exists, and these

classification scales could be improved to better describe the grades of reaction and the subsequent treatment modalities per grade.

The final chapters of this thesis explore transcutaneous systems. Although transcutaneous systems like the Sophono^{TM} offer appealing benefits, hearing outcomes are suspected to underperform when compared to percutaneous devices due to the dampening of sound due to sound transmission via the skin when compared to percutaneous devices that allow direct coupling via the osseointegrated abutment (Håkansson et al., 1990; Hol et al., 2013). The review revealed functional improvements that seem comparable to previously described methods of hearing restoration by percutaneous devices (Reinfeldt et al., 2015). The major advantage of transcutaneous systems is the intact skin that decreases the risk soft-tissue complications. However, the review showed that although skin penetrating reactions do not occur, necrosis associated with the magnet exists. In order to reduce these complications, authors successfully implemented a device-wearing schedule starting with the lowest magnetic strength at initial fitting, followed by a gradual increase in strength and duration of wearing (O'neil et al., 2014). Transcutaneous systems have their clear benefits to the paediatric population because they do not required no daily skin maintenance, fixture extrusion due to trauma does not occur, shorter time to processor use is recommended and lower revision surgery rates as well as skin complications are reported. Nonetheless, the surgical procedure is more invasive in nature than recent percutaneous implants. Another important factor to consider is that it is not uncommon for pediatric patients requiring auditory implants to have other co-morbidities such as neurological conditions and thus, may required one or repeated magnetic resonance imaging. Consequently, the magnetic components in the magnet-based systems may have practical implications in patients requiring MRI. The distortion on MRI images, risks of demagnetization and risk of adverse effects on the

device's output cannot be ignored. Clinicians should be mindful of this when considering these implant choices. Since the transcutaneous devices are fairly novel, the limited number of implanted patients should be highlighted especially when making comparisons with other devices that have been used over the last two decades. More extensive comparative clinical studies are needed to adequately compare outcomes of various available bone conduction hearing devices.

References

Altuna, X., Navarro, J. J., Palicio, I., & Álvarez, L. (2015). Bone-anchored hearing device surgery: Linear incision without soft tissue reduction. A prospective study. *Acta Otorrinolaringologica Espanola*, *66*(5), 258–263. https://doi.org/10.1016/j.otorri.2014.09.007

Bezdjian, A., Smith, R. A., Thomeer, H. G. X. M., Willie, B. M., & Daniel, S. J. (2018). A systematic review on factors associated with percutaneous bone anchored hearing implants loss. *Otology & Neurotology*, *39*(10), e897-e906. https://doi.org/10.1097/MAO.0000000000002041

Calon, T. G. A., Johansson, M. L., Bruijn, A. J. G. de, van den Berge, H., Wagenaar, M., Eichhorn, E., Janssen, M. M. L., Hof, J. R., Brunings, J.-W., Joore, M. A., Jonhede, S., van Tongeren, J., Holmberg, M., & Stokroos, R.-J. (2018). Minimally invasive ponto surgery versus the linear incision technique with soft tissue preservation for bone conduction hearing implants: A multicenter randomized controlled trial. *Otology & Neurotology*, *39*(7), 882–893. https://doi.org/10.1097/MAO.0000000000001852

Cass, S. P., & Mudd, P. A. (2010). Bone-anchored hearing devices: Indications, outcomes, and the linear surgical technique. *Operative Techniques in Otolaryngology-Head and Neck Surgery*, *21*(3), 197–206. https://doi.org/10.1016/j.otot.2010.05.004

Demontiero, O., Vidal, C., & Duque, G. (2012). Aging and bone loss: New insights for the clinician. *Therapeutic Advances in Musculoskeletal Disease*, *4*(2), 61–76. https://doi.org/10.1177/1759720X11430858

Gapski, R., Wang, H.-L., Mascarenhas, P., & Lang, N. P. (2003). Critical review of immediate implant loading. *Clinical Oral Implants Research*, *14*(5), 515–527. https://doi.org/10.1034/j.1600-0501.2003.00950.x

Goldhahn, J., Suhm, N., Goldhahn, S., Blauth, M., & Hanson, B. (2008). Influence of osteoporosis on fracture fixation--a systematic literature review. *Osteoporosis International*, *19*(6), 761–772. https://doi.org/10.1007/s00198-007-0515-9

Gristina, A. G. (1987). Biomaterial-centered infection: Microbial adhesion versus tissue integration. *Science (New York, N.Y.)*, *237*(4822), 1588–1595. https://doi.org/10.1126/science.3629258

Håkansson, B., Tjellström, A., & Carlsson, P. (1990). Percutaneous vs. Transcutaneous transducers for hearing by direct bone conduction. *Otolaryngology--Head and Neck Surgery*, *102*(4), 339–344. https://doi.org/10.1177/019459989010200407

Hobson, J. C., Roper, A. J., Andrew, R., Rothera, M. P., Hill, P., & Green, K. M. (2010). Complications of bone-anchored hearing aid implantation. *The Journal of Laryngology and Otology*, *124*(2), 132–136. https://doi.org/10.1017/S0022215109991708

Høgsbro, M., Agger, A., & Johansen, L. V. (2017). Successful loading of a bone-anchored hearing implant at 1 week after surgery. *Otology & Neurotology*, *38*(2), 207–211. https://doi.org/10.1097/MAO.0000000000001312

Hol, M. K. S., Nelissen, R. C., Agterberg, M. J. H., Cremers, C. W. R. J., & Snik, A. F. M. (2013). Comparison between a new implantable transcutaneous bone conductor and percutaneous bone-conduction hearing implant. *Otology & Neurotology*, *34*(6), 1071–1075. https://doi.org/10.1097/MAO.0b013e3182868608

Holgers, K. M., Thomsen, P., Tjellström, A., & Ericson, L. E. (1995). Electron microscopic observations on the soft tissue around clinical long-term percutaneous titanium implants. *Biomaterials*, *16*(2), 83–90. https://doi.org/10.1016/0142-9612(95)98267-i

Holgers, K.-M., Tjellström, A., Bjursten, L. M., & Erlandsson, B.-E. (1988). Soft tissue reactions around percutaneous implants: A clinical study of soft tissue conditions around skin-penetrating titanium implants for bone-anchored hearing aids. *Otology & Neurotology*, *9*(1), 56–63.

Hultcrantz, M. (2015). Stability testing of a wide bone-anchored device after surgery without skin thinning. *BioMed Research International*, *2015*, 853072. https://doi.org/10.1155/2015/853072

Katsoulis, J., Avrampou, M., Spycher, C., Stipic, M., Enkling, N., & Mericske-Stern, R. (2012). Comparison of implant stability by means of resonance frequency analysis for flapless and conventionally inserted implants. *Clinical Implant Dentistry and Related Research*, *14*(6), 915–923. https://doi.org/10.1111/j.1708-8208.2010.00326.x

Kim, W. Y., Han, C. H., Park, J. I., & Kim, J. Y. (2001). Failure of intertrochanteric fracture fixation with a dynamic hip screw in relation to pre-operative fracture stability and osteoporosis. *International Orthopaedics*, *25*(6), 360–362. https://doi.org/10.1007/s002640100287

Kiringoda, R., & Lustig, L. R. (2013). A meta-analysis of the complications associated with osseointegrated hearing aids. *Otology & Neurotology*, *34*(5), 790–794. https://doi.org/10.1097/MAO.0b013e318291c651

Kruyt, I. J., Banga, R., Banerjee, A., Mylanus, E. A. M., & Hol, M. K. S. (2018). Clinical evaluation of a new laser-ablated titanium implant for bone-anchored hearing in 34

patients: 1-year experience. *Clinical Otolaryngology*, *43*(2), 761–764. https://doi.org/10.1111/coa.13060

Larsson, A., Tjellström, A., & Stalfors, J. (2015). Implant losses for the bone-anchored hearing devices are more frequent in some patients. *Otology & Neurotology*, *36*(2), 336–340. https://doi.org/10.1097/MAO.0000000000000446

Marquezan, M., Osório, A., Sant'Anna, E., Souza, M. M., & Maia, L. (2012). Does bone mineral density influence the primary stability of dental implants? A systematic review. *Clinical Oral Implants Research*, *23*(7), 767–774. https://doi.org/10.1111/j.1600-0501.2011.02228.x

Meredith, N. (1998). Assessment of implant stability as a prognostic determinant. *The International Journal of Prosthodontics*, *11*(5), 491–501.

Merheb, J., Temmerman, A., Rasmusson, L., Kübler, A., Thor, A., & Quirynen, M. (2016). Influence of skeletal and local bone density on dental implant stability in patients with osteoporosis. *Clinical Implant Dentistry and Related Research*, *18*(2), 253–260. https://doi.org/10.1111/cid.12290

Merheb, J., Vercruyssen, M., Coucke, W., & Quirynen, M. (2018). Relationship of implant stability and bone density derived from computerized tomography images. *Clinical Implant Dentistry and Related Research*, *20*(1), 50–57. https://doi.org/10.1111/cid.12579

Mohamad, S., Khan, I., Hey, S. Y., & Hussain, S. S. M. (2016). A systematic review on skin complications of bone-anchored hearing aids in relation to surgical techniques. *European Archives of Oto-Rhino-Laryngology*, *273*(3), 559–565. https://doi.org/10.1007/s00405-014-3436-1

Nelissen, R. C., Wigren, S., Flynn, M. C., Meijer, G. J., Mylanus, E. A. M., & Hol, M. K. S. (2015). Application and interpretation of resonance frequency analysis in auditory osseointegrated implants: A review of literature and establishment of practical recommendations. *Otology & Neurotology*, *36*(9), 1518–1524. https://doi.org/10.1097/MAO.0000000000000833

O'Niel, M. B., Runge, C. L., Friedland, D. R., & Kerschner, J. E. (2014). Patient outcomes in magnet-based implantable auditory assist devices. *JAMA Otolaryngology-- Head & Neck Surgery*, *140*(6), 513–520. https://doi.org/10.1001/jamaoto.2014.484

PILLIAR, R. M., LEE, J. M., & MANIATOPOULOS, C. (1986). Observations on the effect of movement on bone ingrowth into porous-surfaced implants. *Clinical Orthopaedics and Related Research*, *&NA;*(208), 108???113. https://doi.org/10.1097/00003086-198607000-00023

Razi, H., Birkhold, A. I., Weinkamer, R., Duda, G. N., Willie, B. M., & Checa, S. (2015). Aging leads to a dysregulation in mechanically driven bone formation and resorption. *Journal of Bone and Mineral Research*, *30*(10), 1864–1873. https://doi.org/10.1002/jbmr.2528

Reinfeldt, S., Håkansson, B., Taghavi, H., & Eeg-Olofsson, M. (2015). New developments in bone-conduction hearing implants: A review. *Medical Devices (Auckland, N.Z.)*, *8*, 79–93. https://doi.org/10.2147/MDER.S39691

Sclar, A. G. (2007). Guidelines for flapless surgery. *Journal of Oral and Maxillofacial Surgery*, *65*(7 Suppl 1), 20–32. https://doi.org/10.1016/j.joms.2007.03.017

Sennerby, L., & Meredith, N. (2008). Implant stability measurements using resonance frequency analysis: Biological and biomechanical aspects and clinical implications. *Periodontology 2000*, *47*, 51–66. https://doi.org/10.1111/j.1600-0757.2008.00267.x

Willie, B. M., Yang, X., Kelly, N. H., Han, J., Nair, T., Wright, T. M., van der Meulen, M. C. H., & Bostrom, M. P. G. (2010). Cancellous bone osseointegration is enhanced by in vivo loading. *Tissue Engineering. Part C, Methods*, *16*(6), 1399–1406. https://doi.org/10.1089/ten.tec.2009.0776

Chapter 7

Future perspectives

This thesis highlights the latest surgical innovations of bone anchored hearing systems and discusses novel ways to determine the integrity of the bone-implant interface to facilitate clinical decisions. Included in this thesis are outcomes gathered from laboratory experiments on cadavers, retrospective cohorts, comparative studies, systematic reviews and reliability assessments.

Surgical innovations are continuously being refined and novel ones being implemented. The aim of future surgical approaches to bone anchored hearing systems should aim to reduce or remove anesthesia use making the procedure entirely at the out-patient clinic. Moreover, innovative surgical approaches should aim at the reduction in surgical duration and post-operative complications. Treatment algorithms based on objective and standardised assessment of skin tolerability should be implemented using improved classification scales. The aftercare and maintenance regimes should be minimized and standardized by predefined follow up protocols. Novel implant coatings and screw surface modifications could lead to reduced skin reaction and implant extrusions.

Novel diagnostic technologies could permit the development of an assessment tool to determine the skull bone thickness and quality pre-operatively. This will aid surgeons decide where to drill in the temporoparietal skull region to place the implant in an optimal host bone location, particularly of interest to children and syndromic patient who could present with compromised skull bones. Surgical approaches with integrated sound processor coupling protocols should be explored since early evidence shows the micromotion is limited and does not affect stability.

The relationship between clinical, microbiological and molecular outcomes following bone anchored hearing implant surgeries should further be explored to understand and improve key

determinants playing a role in bone-implant fixation. Further investigation aimed at the development of the temporoparietal skull bone could promote early implantation protocols.

Finally, the advantages of passive and active transcutaneous systems should be further explored to highlight the long-term benefits and quality of life improvement of these devices. Implant transducers should be reduced in size to reduce implant related surgical challenges and allow implantation in younger patients.

Chapter 8

References

Aitkin, L. M., Webster, W. R., Veale, J. L., & Crosby, D. C. (1975). Inferior colliculus. I. Comparison of response properties of neurons in central, pericentral, and external nuclei of adult cat. *Journal of Neurophysiology*, *38*(5), 1196–1207. https://doi.org/10.1152/jn.1975.38.5.1196

Akagawa, Y., Hashimoto, M., Kondo, N., Satomi, K., Takata, T., & Tsuru, H. (1986). Initial bone-implant interfaces of submergible and supramergible endosseous single-crystal sapphire implants. *The Journal of Prosthetic Dentistry*, *55*(1), 96–100. https://doi.org/10.1016/0022-3913(86)90083-1

Akagawa, Y., Ichikawa, Y., Nikai, H., & Tsuru, H. (1993). Interface histology of unloaded and early loaded partially stabilized zirconia endosseous implant in initial bone healing. *The Journal of Prosthetic Dentistry*, *69*(6), 599–604. https://doi.org/10.1016/0022-3913(93)90289-Z

Al-Bashaireh, A. M., Haddad, L. G., Weaver, M., Chengguo, X., Kelly, D. L., & Yoon, S. (2018). The effect of tobacco smoking on bone mass: An overview of pathophysiologic mechanisms. *Journal of Osteoporosis*, *2018*, 1206235. https://doi.org/10.1155/2018/1206235

Albrektsson, T., Brånemark, P. I., Hansson, H. A., & Lindström, J. (1981). Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man. *Acta Orthopaedica Scandinavica*, *52*(2), 155–170. https://doi.org/10.3109/17453678108991776

Almukhtar, Nar. (2018). Chapter two: Literature review. In book: *Electrophysiological assessment for children with sensorineural hearing impairment.*

Altuna, X., Navarro, J. J., Palicio, I., & Álvarez, L. (2015). Bone-anchored hearing device surgery: Linear incision without soft tissue reduction. A prospective study. *Acta Otorrinolaringologica Espanola*, *66*(5), 258–263. https://doi.org/10.1016/j.otorri.2014.09.007

Amonoo-Kuofi, K., Kelly, A., Neeff, M., & Brown, C. R. S. (2015). Experience of bone-anchored hearing aid implantation in children younger than 5 years of age. *International Journal of Pediatric Otorhinolaryngology*, *79*(4), 474–480. https://doi.org/10.1016/j.ijporl.2014.12.033

Andersson, P., Pagliani, L., Verrocchi, D., Volpe, S., Sahlin, H., & Sennerby, L. (2019). Factors influencing resonance frequency analysis (RFA) measurements and 5-year survival of neoss dental implants. *International Journal of Dentistry*, *2019*, 3209872. https://doi.org/10.1155/2019/3209872

Apostu, D., Lucaciu, O., Berce, C., Lucaciu, D., & Cosma, D. (2017). Current methods of preventing aseptic loosening and improving osseointegration of titanium implants in cementless total hip arthroplasty: A review. *The Journal of International Medical Research*, *46*(6), 2104–2119. https://doi.org/10.1177/0300060517732697

Ashmore, J., & Géléoc, G. S. (1999). Cochlear function: Hearing in the fast lane. *Current Biology*, *9*(15), R572-R574. https://doi.org/10.1016/S0960-9822(99)80358-3

Bain, C. A., & Moy, P. K. (1993). The association between the failure of dental implants and cigarette smoking. *Int J Oral Maxillofac Implants*, *8*(6), 609–615.

Baker, A. R., Fanelli, D. G., Kanekar, S., & Isildak, H. (2017). A retrospective review of temporal bone imaging with respect to bone-anchored hearing aid placement. *Otology & Neurotology* , *38*(1), 86–88. https://doi.org/10.1097/MAO.0000000000001235

Baker, A., Fanelli, D., Kanekar, S., & Isildak, H. (2016). A review of temporal bone ct imaging with respect to pediatric bone-anchored hearing aid placement. *Otology & Neurotology* , *37*(9), 1366–1369. https://doi.org/10.1097/MAO.0000000000001172

Baker, S., Centric, A., & Chennupati, S. K. (2015). Innovation in abutment-free bone-anchored hearing devices in children: Updated results and experience. *International Journal of Pediatric Otorhinolaryngology*, *79*(10), 1667–1672. https://doi.org/10.1016/j.ijporl.2015.07.021

Barbara, M., Perotti, M., Gioia, B., Volpini, L., & Monini, S. (2013). Transcutaneous bone-conduction hearing device: Audiological and surgical aspects in a first series of patients with mixed hearing loss. *Acta Oto-Laryngologica*, *133*(10), 1058–1064. https://doi.org/10.3109/00016489.2013.799293

Barrett, K. E., Barman, S. M., Boitano, S., & Brooks, H. L. (2012). *Ganong's review of medical physiology* (24th ed.). McGraw Hill Medical.

Bayliss, L., Mahoney, D. J., & Monk, P. (2012). Normal bone physiology, remodelling and its hormonal regulation. *Surgery (Oxford)*, *30*(2), 47–53. https://doi.org/10.1016/j.mpsur.2011.12.009

Bear, M. F., Connors, B. W., & Paradiso, M. A. (2007). *Neuroscience Exploring the brain*. Lippincott Williams & Wilkins.

Bellido, T., Plotkin, L. I., & Bruzzaniti, A. (2019). Bone cells. In *Basic and Applied Bone Biology* (pp. 37–55). Elsevier. https://doi.org/10.1016/B978-0-12-813259-3.00003-8

Bernardeschi, D., Russo, F. Y., Nguyen, Y., Vicault, E., Flament, J., Bernou, D., Sterkers, O., & Mosnier, I. (2016). Audiological results and quality of life of sophono alpha 2

transcutaneous bone-anchored implant users in single-sided deafness. *Audiology & Neuro-Otology*, *21*(3), 158–164. https://doi.org/10.1159/000445344

Bess, F. H., & Humes, L. (2008). *Audiology: the fundamentals*. Lippincott Williams & Wilkins.

Bezdjian, A., Smith, R. A., Gabra, N., Yang, L., Bianchi, M., & Daniel, S. J. (2020). Experience with minimally invasive ponto surgery and linear incision approach for pediatric and adult bone anchored hearing implants. *The Annals of Otology, Rhinology, and Laryngology*, *129*(4), 380–387. https://doi.org/10.1177/0003489419891451

Bezdjian, A., Smith, R. A., Thomeer, H. G. X. M., Willie, B. M., & Daniel, S. J. (2018). A systematic review on factors associated with percutaneous bone anchored hearing implants loss. *Otology & Neurotology* , *39*(10), e897-e906. https://doi.org/10.1097/MAO.0000000000002041

Biskobing, D. M. (2002). COPD and osteoporosis. *Chest*, *121*(2), 609–620. https://doi.org/10.1378/chest.121.2.609

Botella, J. (n.d.). What is an audiogram and how to read it. *Hear*. https://www.hear.com/resources/all-articles/what-is-audiogram-how-to-read-it/

Brånemark, P. I., Hansson, B. O., Adell, R., Breine, U., Lindström, J., Hallén, O., & Ohman, A. (1977). Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period. *Scandinavian Journal of Plastic and Reconstructive Surgery. Supplementum*, *16*, 1–132.

Brånemark, P. I., Zarb, G. A., & Albrektsson, T. (1985). *Tissue-Integrated Prostheses: Osseointegration in Clinical Dentistry*. Quintessence Publishing Company Inc.

Branemark, P.-I. (1983). Osseointegration and its experimental background. *The Journal of Prosthetic Dentistry*, *50*(3), 399–410. https://doi.org/10.1016/S0022-3913(83)80101-2

Brant, J. A., Gudis, D., & Ruckenstein, M. J. (2013). Results of baha® implantation using a small horizontal incision. *American Journal of Otolaryngology*, *34*(6), 641–645. https://doi.org/10.1016/j.amjoto.2013.07.005

Bridges, J. A., & Bentler, R. A. (1998). Relating hearing aid use to well-being among older adults. *The Hearing Journal*, *51*(7), 39. https://doi.org/10.1097/00025572-199807000-00002

Britannica. (2013). Bone remodeling. In *Encyclopædia Britannica.* https://www.britannica.com/science/bone-remodeling

Brunski, J. B. (1992). Biomechanical factors affecting the bone-dental implant interface. *Clinical Materials*, *10*(3), 153–201. https://doi.org/10.1016/0267-6605(92)90049-Y

Brunski, J. B., Moccia, A. F., Pollack, S. R., Korostoff, E., & Trachtenberg, D. I. (1979). The influence of functional use of endosseous dental implants on the tissue-implant interface. I. Histological aspects. *Journal of Dental Research*, *58*(10), 1953–1969. https://doi.org/10.1177/00220345790580100201

Buckwalter, J. A., Glimcher, M. J., Cooper, R. R., & Recker, R. (1995). Bone biology. *The Journal of Bone & Joint Surgery*, *77*(8), 1256–1275. https://doi.org/10.2106/00004623-199508000-00019

Buckwalter, J. A., Glimcher, M. J., Cooper, R. R., & Recker, R. (1996). Bone biology. II: Formation, form, modeling, remodeling, and regulation of cell function. *Instructional Course Lectures*, *45*, 387–399.

Burr, D. B. (2019). Bone morphology and organization. In *Basic and Applied Bone Biology* (pp. 3–26). Elsevier. https://doi.org/10.1016/B978-0-12-813259-3.00001-4

Çakatay, U., Telci, A., Kayalı, R., Akçay, T., Sivas, A., & Aral, F. (1998). Changes in bone turnover on deoxypyridinoline levels in diabetic patients. *Diabetes Research and Clinical Practice*, *40*(2), 75–79. https://doi.org/10.1016/S0168-8227(98)00025-4

Calon, T. G. A., Johansson, M. L., Bruijn, A. J. G. de, van den Berge, H., Wagenaar, M., Eichhorn, E., Janssen, M. M. L., Hof, J. R., Brunings, J.-W., Joore, M. A., Jonhede, S., van Tongeren, J., Holmberg, M., & Stokroos, R.-J. (2018). Minimally invasive ponto surgery versus the linear incision technique with soft tissue preservation for bone conduction hearing implants: A multicenter randomized controlled trial. *Otology & Neurotology* , *39*(7), 882–893. https://doi.org/10.1097/MAO.0000000000001852

Calvo Bodnia, N., Foghsgaard, S., Nue Møller, M., & Cayé-Thomasen, P. (2014). Long-term results of 185 consecutive osseointegrated hearing device implantations: A comparison among children, adults, and elderly. *Otology & Neurotology* , *35*(10), e301-6. https://doi.org/10.1097/MAO.0000000000000543

Cameron, H. U., Pilliar, R. M., & MacNab, I. (1973). The effect of movement on the bonding of porous metal to bone. *Journal of Biomedical Materials Research*, *7*(4), 301–311. https://doi.org/10.1002/jbm.820070404

Carr, S. D., Moraleda, J., Baldwin, A., & Ray, J. (2016). Bone-conduction hearing aids in an elderly population: Complications and quality of life assessment. *European Archives of Oto-Rhino-Laryngology*, *273*(3), 567–571. https://doi.org/10.1007/s00405-015-3574-0

Cass, S. P., & Mudd, P. A. (2010). Bone-anchored hearing devices: Indications, outcomes, and the linear surgical technique. *Operative Techniques in Otolaryngology-Head and Neck Surgery*, *21*(3), 197–206. https://doi.org/10.1016/j.otot.2010.05.004

Chan, G. K., & Duque, G. (2002). Age-related bone loss: Old bone, new facts. *Gerontology*, *48*(2), 62–71. https://doi.org/10.1159/000048929

Chrcanovic, B. R., Kisch, J., Albrektsson, T., & Wennerberg, A. (2016). Factors influencing early dental implant failures. *Journal of Dental Research*, *95*(9), 995–1002. https://doi.org/10.1177/0022034516646098

Cutrim, D. M. S. L., Pereira, F. A., Paula, F. J. A. de, & Foss, M. C. (2007). Lack of relationship between glycemic control and bone mineral density in type 2 diabetes mellitus. *Brazilian Journal of Medical and Biological Research*, *40*(2), 221–227. https://doi.org/10.1590/S0100-879X2007000200008

Davies, J. E. (2003). Understanding peri-implant endosseous healing. *Journal of Dental Education*, *67*(8), 932–949. https://doi.org/10.1002/j.0022-0337.2003.67.8.tb03681.x

de Wolf, M. J. F., Hol, M. K. S., Huygen, P. L. M., Mylanus, E. A. M., & Cremers, C. W. R. J. (2008). Clinical outcome of the simplified surgical technique for BAHA implantation. *Otology & Neurotology* , *29*(8), 1100–1108. https://doi.org/10.1097/MAO.0b013e31818599b8

de Wolf, M. J. F., Hol, M. K. S., Huygen, P. L. M., Mylanus, E. A. M., & Cremers, C. W. R. J. (2008). Nijmegen results with application of a bone-anchored hearing aid in children: Simplified surgical technique. *The Annals of Otology, Rhinology, and Laryngology*, *117*(11), 805–814. https://doi.org/10.1177/000348940811701103

de Wolf, M. J. F., Hol, M. K. S., Mylanus, E. A. M., & Cremers, C. W. R. J. (2009). Bone-anchored hearing aid surgery in older adults: Implant loss and skin reactions. *The Annals of Otology, Rhinology, and Laryngology*, *118*(7), 525–531. https://doi.org/10.1177/000348940911800712

Delye, H., Clijmans, T., Mommaerts, M. Y., Sloten, J. V., & Goffin, J. (2015). Creating a normative database of age-specific 3d geometrical data, bone density, and bone thickness of the developing skull: A pilot study. *Journal of Neurosurgery. Pediatrics*, *16*(6), 687–702. https://doi.org/10.3171/2015.4.PEDS1493

Demontiero, O., Vidal, C., & Duque, G. (2012). Aging and bone loss: New insights for the clinician. *Therapeutic Advances in Musculoskeletal Disease*, *4*(2), 61–76. https://doi.org/10.1177/1759720X11430858

den Besten, C. A., Bosman, A. J., Nelissen, R. C., Mylanus, E. A. M., & Hol, M. K. S. (2016). Controlled clinical trial on bone-anchored hearing implants and a surgical technique with soft-tissue preservation. *Otology & Neurotology* , *37*(5), 504–512. https://doi.org/10.1097/MAO.0000000000000994

den Besten, C. A., Nelissen, R. C., Peer, P. G. M., Faber, H. T., Dun, C. A. J., de Wolf, M. J. F., Kunst, H. P. M., Cremers, C. W. R. J., Mylanus, E. A. M., & Hol, M. K. S. (2015). A retrospective cohort study on the influence of comorbidity on soft tissue reactions, revision surgery, and implant loss in bone-anchored hearing implants. *Otology & Neurotology* , *36*(5), 812–818. https://doi.org/10.1097/MAO.0000000000000745

den Besten, C. A., Stalfors, J., Wigren, S., Blechert, J. I., Flynn, M., Eeg-Olofsson, M., Aggarwal, R., Green, K., Nelissen, R. C., Mylanus, E. A. M., & Hol, M. K. S. (2016). Stability, survival, and tolerability of an auditory osseointegrated implant for bone conduction hearing: Long-term follow-up of a randomized controlled trial. *Otology & Neurotology* , *37*(8), 1077–1083. https://doi.org/10.1097/MAO.0000000000001111

Denoyelle, F., Coudert, C., Thierry, B., Parodi, M., Mazzaschi, O., Vicaut, E., Tessier, N., Loundon, N., & Garabedian, E.-N. (2015). Hearing rehabilitation with the closed skin

bone-anchored implant sophono alpha1: Results of a prospective study in 15 children with ear atresia. *International Journal of Pediatric Otorhinolaryngology*, *79*(3), 382–387. https://doi.org/10.1016/j.ijporl.2014.12.032

Deporter, D. A., Watson, P. A., Pilliar, R. M., Chipman, M. L., & Valiquette, N. (1990). A histological comparison in the dog of porous-coated vs. Threaded dental implants. *Journal of Dental Research*, *69*(5), 1138–1145. https://doi.org/10.1177/00220345900690050401

Doshi, J., McDermott, A.-L., Reid, A., & Proops, D. (2010). The use of a bone-anchored hearing aid (baha) in children with severe behavioural problems--the birmingham baha programme experience. *International Journal of Pediatric Otorhinolaryngology*, *74*(6), 608–610. https://doi.org/10.1016/j.ijporl.2010.03.002

Doshi, J., Sheehan, P., & McDermott, A. L. (2012). Bone anchored hearing aids in children: An update. *International Journal of Pediatric Otorhinolaryngology*, *76*(5), 618–622. https://doi.org/10.1016/j.ijporl.2012.02.030

Drinias, V., Granström, G., & Tjellström, A. (2007). High age at the time of implant installation is correlated with increased loss of osseointegrated implants in the temporal bone. *Clinical Implant Dentistry and Related Research*, *9*(2), 94–99. https://doi.org/10.1111/j.1708-8208.2007.00047.x

Ducheyne, P., Meester, P. de, & Aernoudt, E. (1977). Influence of a functional dynamic loading on bone ingrowth into surface pores of orthopedic implants. *Journal of Biomedical Materials Research*, *11*(6), 811–838. https://doi.org/10.1002/jbm.820110603

Dumon, T., Medina, M., & Sperling, N. M. (2016). Punch and drill: Implantation of bone anchored hearing device through a minimal skin punch incision versus implantation with

dermatome and soft tissue reduction. *The Annals of Otology, Rhinology, and Laryngology*, *125*(3), 199–206. https://doi.org/10.1177/0003489415606447

Dun, C. A. J., Faber, H. T., Wolf, M. J. F. de, Mylanus, E. A. M., Cremers, C. W. R. J., & Hol, M. K. S. (2012). Assessment of more than 1,000 implanted percutaneous bone conduction devices: Skin reactions and implant survival. *Otology & Neurotology*, *33*(2), 192–198. https://doi.org/10.1097/MAO.0b013e318241c0bf

Dun, C. A. J., Wolf, M. J. F. de, Hol, M. K. S., Wigren, S., Eeg-Olofsson, M., Green, K., Karlsmo, A., Flynn, M. C., Stalfors, J., Rothera, M., Mylanus, E. A. M., & Cremers, C. W. R. J. (2011). Stability, survival, and tolerability of a novel baha implant system: Six-month data from a multicenter clinical investigation. *Otology & Neurotology*, *32*(6), 1001–1007. https://doi.org/10.1097/MAO.0b013e3182267e9c

Edmiston, R. C., Aggarwal, R., & Green, K. M. J. (2015). Bone conduction implants - a rapidly developing field. *The Journal of Laryngology and Otology*, *129*(10), 936–940. https://doi.org/10.1017/S0022215115002042

Ellingsen, J. E., & Lyngstadaas, S. P. (2003). *Bio-Implant Interface*. CRC Press. https://doi.org/10.1201/9780203491430

Escorihuela-García, V., Llópez-Carratalá, I., Pitarch-Ribas, I., Latorre-Monteagudo, E., & Marco-Algarra, J. (2014). Initial experience with the sophono alpha 1 osseointegrated implant. *Acta Otorrinolaringologica Espanola*, *65*(6), 361–364. https://doi.org/10.1016/j.otorri.2014.01.005

Esposito, M., Hirsch, J. M., Lekholm, U., & Thomsen, P. (1998). Biological factors contributing to failures of osseointegrated oral implants. (I). Success criteria and epidemiology.

European Journal of Oral Sciences, *106*(1), 527–551. https://doi.org/10.1046/j.0909-8836.t01-2-.x

Esposito, M., Hirsch, J., Lekholm, U., & Thomsen, P. (1999). Differential diagnosis and treatment strategies for biologic complications and failing oral implants: A review of the literature. *Int J Oral Maxillofac Implants*, *14*(4), 473–490.

Falland-Cheung, L., Waddell, J. N., Chun Li, K., Tong, D., & Brunton, P. (2017). Investigation of the elastic modulus, tensile and flexural strength of five skull simulant materials for impact testing of a forensic skin/skull/brain model. *Journal of the Mechanical Behavior of Biomedical Materials*, *68*, 303–307. https://doi.org/10.1016/j.jmbbm.2017.02.023

Ferguson, L., & MacAndie, C. (2016). From the bathroom to the bone-anchored hearing aid: An idea on how to remove a stripped abutment screw from a bone-anchored hearing aid. *Clinical Otolaryngology*, *41*(5), 620–621. https://doi.org/10.1111/coa.12446

FirstYears. (n.d.). http://firstyears.org/anatomy/ear.htm

Fontaine, N., Hemar, P., Schultz, P., Charpiot, A., & Debry, C. (2014). BAHA implant: Implantation technique and complications. *European Annals of Otorhinolaryngology, Head and Neck Diseases*, *131*(1), 69–74. https://doi.org/10.1016/j.anorl.2012.10.006

Gapski, R., Wang, H.-L., Mascarenhas, P., & Lang, N. P. (2003). Critical review of immediate implant loading. *Clinical Oral Implants Research*, *14*(5), 515–527. https://doi.org/10.1034/j.1600-0501.2003.00950.x

Gelfand, S. A. (2009). *Essentials of audiology*. Thiem.

Ghanem, A., Abduljabbar, T., Akram, Z., Vohra, F., Kellesarian, S. V., & Javed, F. (2017). A systematic review and meta-analysis of pre-clinical studies assessing the effect of

nicotine on osseointegration. *International Journal of Oral and Maxillofacial Surgery*, *46*(4), 496–502. https://doi.org/10.1016/j.ijom.2016.12.003

Glüer, C. C., Blake, G., Lu, Y., Blunt, B. A., Jergas, M., & Genant, H. K. (1995). Accurate assessment of precision errors: How to measure the reproducibility of bone densitometry techniques. *Osteoporosis International*, *5*(4), 262–270. https://doi.org/10.1007/BF01774016

Goldhahn, J., Suhm, N., Goldhahn, S., Blauth, M., & Hanson, B. (2008). Influence of osteoporosis on fracture fixation--a systematic literature review. *Osteoporosis International*, *19*(6), 761–772. https://doi.org/10.1007/s00198-007-0515-9

Goldman, R. A., Georgolios, A., & Shaia, W. T. (2013). The punch method for bone-anchored hearing aid placement. *Otolaryngology--Head and Neck Surgery*, *148*(5), 878–880. https://doi.org/10.1177/0194599813476666

Gordon, S. A., & Coelho, D. H. (2015). Minimally invasive surgery for osseointegrated auditory implants: A comparison of linear versus punch techniques. *Otolaryngology--Head and Neck Surgery*, *152*(6), 1089–1093. https://doi.org/10.1177/0194599815571532

Granström, G. (2003). Radiotherapy, osseointegration and hyperbaric oxygen therapy. *Periodontology 2000*, *33*, 145–162. https://doi.org/10.1046/j.0906-6713.2002.03312.x

Granström, G. (2005). Osseointegration in irradiated cancer patients: An analysis with respect to implant failures. *Journal of Oral and Maxillofacial Surgery*, *63*(5), 579–585. https://doi.org/10.1016/j.joms.2005.01.008

Granström, G., Bergström, K., Odersjö, M., & Tjellström, A. (2001). Osseointegrated implants in children: Experience from our first 100 patients. *Otolaryngology--Head and Neck Surgery*, *125*(1), 85–92. https://doi.org/10.1067/mhn.2001.116190

Granström, G., Tjellström, A., & Albrektsson, T. (1993). Postimplantation irradiation for head and neck cancer treatment. *Int J Oral Maxillofac Implants*, *8*(5), 495–501.

Gristina, A. G. (1987). Biomaterial-centered infection: Microbial adhesion versus tissue integration. *Science (New York, N.Y.)*, *237*(4822), 1588–1595. https://doi.org/10.1126/science.3629258

Guler, A. U., Sumer, M., Duran, I., Sandikci, E. O., & Telcioglu, N. T. (2013). Resonance frequency analysis of 208 straumann dental implants during the healing period. *The Journal of Oral Implantology*, *39*(2), 161–167. https://doi.org/10.1563/AAID-JOI-D-11-00060

Håkansson, B., Eeg-Olofsson, M., Reinfeldt, S., Stenfelt, S., & Granström, G. (2008). Percutaneous versus transcutaneous bone conduction implant system: A feasibility study on a cadaver head. *Otology & Neurotology*, *29*(8), 1132–1139. https://doi.org/10.1097/MAO.0b013e31816fdc90

Håkansson, B., Reinfeldt, S., Persson, A.-C., Jansson, K.-J. F., Rigato, C., Hultcrantz, M., & Eeg-Olofsson, M. (2019). The bone conduction implant - a review and 1-year follow-up. *International Journal of Audiology*, *58*(12), 945–955. https://doi.org/10.1080/14992027.2019.1657243

Håkansson, B., Tjellström, A., & Carlsson, P. (1990). Percutaneous vs. Transcutaneous transducers for hearing by direct bone conduction. *Otolaryngology--Head and Neck Surgery*, *102*(4), 339–344. https://doi.org/10.1177/019459989010200407

Håkansson, B., Tjellström, A., & Rosenhall, U. (1984). Hearing thresholds with direct bone conduction versus conventional bone conduction. *Scandinavian Audiology*, *13*(1), 3–13. https://doi.org/10.3109/01050398409076252

Hashimoto, M., Akagawa, Y., Nikai, H., & Tsuru, H. (1988). Single-crystal sapphire endosseous dental implant loaded with functional stress--clinical and histological evaluation of peri-implant tissues. *Journal of Oral Rehabilitation*, *15*(1), 65–76. https://doi.org/10.1111/j.1365-2842.1988.tb00147.x

Hawley, K., & Haberkamp, T. J. (2013). Osseointegrated hearing implant surgery: Outcomes using a minimal soft tissue removal technique. *Otolaryngology--Head and Neck Surgery*, *148*(4), 653–657. https://doi.org/10.1177/0194599812473414

Healthfavo. (2014). *Inner ear bones*. http://healthfavo.com/inner-ear-bones.html

Hill, C. A. (2011). Ontogenetic change in temporal bone pneumatization in humans. *Anatomical Record*, *294*(7), 1103–1115. https://doi.org/10.1002/ar.21404

Hobson, J. C., Roper, A. J., Andrew, R., Rothera, M. P., Hill, P., & Green, K. M. (2010). Complications of bone-anchored hearing aid implantation. *The Journal of Laryngology and Otology*, *124*(2), 132–136. https://doi.org/10.1017/S0022215109991708

Høgsbro, M., Agger, A., & Johansen, L. V. (2015). Bone-anchored hearing implant surgery: Randomized trial of dermatome versus linear incision without soft tissue reduction--clinical measures. *Otology & Neurotology*, *36*(5), 805–811. https://doi.org/10.1097/MAO.0000000000000731

Høgsbro, M., Agger, A., & Johansen, L. V. (2015). Successful loading of a bone-anchored hearing implant at two weeks after surgery: Randomized trial of two surgical methods and detailed stability measurements. *Otology & Neurotology*, *36*(2), e51-7. https://doi.org/10.1097/MAO.0000000000000647

Høgsbro, M., Agger, A., & Johansen, L. V. (2017). Successful loading of a bone-anchored hearing implant at 1 week after surgery. *Otology & Neurotology*, *38*(2), 207–211. https://doi.org/10.1097/MAO.0000000000001312

Hol, M. K. S., Nelissen, R. C., Agterberg, M. J. H., Cremers, C. W. R. J., & Snik, A. F. M. (2013). Comparison between a new implantable transcutaneous bone conductor and percutaneous bone-conduction hearing implant. *Otology & Neurotology*, *34*(6), 1071–1075. https://doi.org/10.1097/MAO.0b013e3182868608

Holgers, K. M., Thomsen, P., Tjellström, A., & Ericson, L. E. (1995). Electron microscopic observations on the soft tissue around clinical long-term percutaneous titanium implants. *Biomaterials*, *16*(2), 83–90. https://doi.org/10.1016/0142-9612(95)98267-i

Holgers, K. M., Tjellstrom, A., Bjursten, L. M., & Erlandsson, B. E. (1988). Soft tissue reactions around percutaneous implants: A clinical study of soft tissue conditions around skin-penetrating titanium implants for bone-anchored hearing aids. *Am J Otol*, *9*, 56–59.

Holgers, K.-M. (2000). Characteristics of the inflammatory process around skin-penetrating titanium implants for aural rehabilitation: Características del proceso inflamatorio en piel alrededor de los implantes de titanio para la rehabilitatión auditiva. *International Journal of Audiology*, *39*(5), 253–259. https://doi.org/10.3109/00206090009073089

Holgers, K.-M., Tjellström, A., Bjursten, L. M., & Erlandsson, B.-E. (1988). Soft tissue reactions around percutaneous implants: A clinical study of soft tissue conditions around skin-penetrating titanium implants for bone-anchored hearing aids. *Otology & Neurotology*, *9*(1), 56–63.

Hollinger, J. O., Schmitt, J. M., Hwang, K., Soleymani, P., & Buck, D. (1999). Impact of nicotine on bone healing. *Journal of Biomedical Materials Research*, *45*(4), 294–301. https://doi.org/10.1002/(SICI)1097-4636(19990615)45:4<294::AID-JBM3>3.0.CO;2-1

Horstink, L., Faber, H. T., Wolf, M. J. F. de, Dun, C. A. J., Cremers, C. W. R. J., & Hol, M. K. S. (2012). Titanium fixtures for bone-conduction devices and the influence of type 2 diabetes mellitus. *Otology & Neurotology*, *33*(6), 1013–1017. https://doi.org/10.1097/MAO.0b013e318259b36c

Hudspeth, A. J. (1989). How the ear's works work. *Nature*, *341*(6241), 397–404. https://doi.org/10.1038/341397a0

Hudspeth, A. J. (1992). Hair-bundle mechanics and a model for mechanoelectrical transduction by hair cells. *Society of General Physiologists Series*, *47*, 357–370.

Hultcrantz, M. (2011). Outcome of the bone-anchored hearing aid procedure without skin thinning: A prospective clinical trial. *Otology & Neurotology*, *32*(7), 1134–1139. https://doi.org/10.1097/MAO.0b013e31822a1c47

Hultcrantz, M. (2015). Stability testing of a wide bone-anchored device after surgery without skin thinning. *BioMed Research International*, *2015*, 853072. https://doi.org/10.1155/2015/853072

Hultcrantz, M., & Lanis, A. (2014). A five-year follow-up on the osseointegration of bone-anchored hearing device implantation without tissue reduction. *Otology & Neurotology*, *35*(8), 1480–1485. https://doi.org/10.1097/MAO.0000000000000352

Husseman, J., Szudek, J., Monksfield, P., Power, D., O'Leary, S., & Briggs, R. (2013). Simplified bone-anchored hearing aid insertion using a linear incision without soft tissue

reduction. *The Journal of Laryngology and Otology*, *127 Suppl 2*, S33-8. https://doi.org/10.1017/S0022215113000741

Ihde, S., Kopp, S., Gundlach, K., & Konstantinović, V. S. (2009). Effects of radiation therapy on craniofacial and dental implants: A review of the literature. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, *107*(1), 56–65. https://doi.org/10.1016/j.tripleo.2008.06.014

Inc, S. (2015). *Medtronic completes acquisition of Sophono*. http://www.sophono.com

Isaacson, B. M., Vance, R. E., Chou, T. G. R., Bloebaum, R. D., Bachus, K. N., & Webster, J. B. (2009). Effectiveness of resonance frequency in predicting orthopedic implant strength and stability in an in vitro osseointegration model. *Journal of Rehabilitation Research and Development*, *46*(9), 1109–1120. https://doi.org/10.1682/JRRD.2009.06.0080

Isaia, G. C., Ardissone, P., Di Stefano, M., Ferrari, D., Martina, V., Porta, M., Tagliabue, M., & Molinatti, G. M. (1999). Bone metabolism in type 2 diabetes mellitus. *Acta Diabetologica*, *36*(1-2), 35–38. https://doi.org/10.1007/s005920050142

Iseri, M., Orhan, K. S., Yarıktaş, M. H., Kara, A., Durgut, M., Ceylan, D. S., Guldiken, Y., Keskin, I. G., & Değer, K. (2015). Surgical and audiological evaluation of the baha BA400. *The Journal of Laryngology and Otology*, *129*(1), 32–37. https://doi.org/10.1017/S0022215114003284

Jahn, A. F., & Santo-Sacchi, J. (2001). *Physiology of the ear*. Cengage Learning.

Jarabin, J., Bere, Z., Hartmann, P., Tóth, F., Kiss, J. G., & Rovó, L. (2015). Laser-doppler microvascular measurements in the peri-implant areas of different osseointegrated bone conductor implant systems. *European Archives of Oto-Rhino-Laryngology*, *272*(12), 3655–3662. https://doi.org/10.1007/s00405-014-3429-0

Johansson, M. L., Stokroos, R. J., Banga, R., Hol, M. K., Mylanus, E. A., Savage Jones, H., Tysome, J. R., Vannucchi, P., Hof, J. R., Brunings, J. W., van Tongeren, J., Lutgert, R. W., Banerjee, A., Windfuhr, J. P., Caruso, A., Giannuzzi, A. L., Bordin, S., Hanif, J., Schart-Morén, N., . . . Hultcrantz, M. (2017). Short-term results from seventy-six patients receiving a bone-anchored hearing implant installed with a novel minimally invasive surgery technique. *Clinical Otolaryngology*, *42*(5), 1043–1048. https://doi.org/10.1111/coa.12803

Johansson, M., & Holmberg, M. *Design and clinical evaluation of MIPS- A new perspective on tissue preservation*. https://www.oticonmedical.com.

Joshi, A., Gray, R., & Mahendran, S. (2006). A novel method to remove worn-out abutment from fixture of bone-anchored hearing aid (BAHA). *Otolaryngology--Head and Neck Surgery*, *135*(4), 631–632. https://doi.org/10.1016/j.otohns.2006.05.749

Kanis, J. A., Johnell, O., Oden, A., Johansson, H., Laet, C. de, Eisman, J. A., Fujiwara, S., Kroger, H., McCloskey, E. V., Mellstrom, D., Melton, L. J., Pols, H., Reeve, J., Silman, A., & Tenenhouse, A. (2005). Smoking and fracture risk: A meta-analysis. *Osteoporosis International*, *16*(2), 155–162. https://doi.org/10.1007/s00198-004-1640-3

Kasat, V., & Ladda, R. (2012). Smoking and dental implants. *Journal of International Society of Preventive & Community Dentistry*, *2*(2), 38–41. https://doi.org/10.4103/2231-0762.109358

Katsoulis, J., Avrampou, M., Spycher, C., Stipic, M., Enkling, N., & Mericske-Stern, R. (2012). Comparison of implant stability by means of resonance frequency analysis for flapless and conventionally inserted implants. *Clinical Implant Dentistry and Related Research*, *14*(6), 915–923. https://doi.org/10.1111/j.1708-8208.2010.00326.x

Katz, J. (Ed.). (2002). *Handbook of clinical audiology* (5th). Lippincott Williams & Wilkins.

Katz, J., & Lezynski, J. (2002). Clinical masking. In J. Katz (Ed.), *Handbook of clinical audiology* (5th ed., pp. 124–141). Lippincott Williams & Wilkins.

Kelion, L. (2013). *Talking train window adverts tested by Sky Deutschland*. BBC. https://www.bbc.com/news/technology-23167112?SThisFB

Kim, W. Y., Han, C. H., Park, J. I., & Kim, J. Y. (2001). Failure of intertrochanteric fracture fixation with a dynamic hip screw in relation to pre-operative fracture stability and osteoporosis. *International Orthopaedics*, *25*(6), 360–362. https://doi.org/10.1007/s002640100287

Kiringoda, R., & Lustig, L. R. (2013). A meta-analysis of the complications associated with osseointegrated hearing aids. *Otology & Neurotology*, *34*(5), 790–794. https://doi.org/10.1097/MAO.0b013e318291c651

Koester, K. J., Barth, H. D., & Ritchie, R. O. (2011). Effect of aging on the transverse toughness of human cortical bone: Evaluation by r-curves. *Journal of the Mechanical Behavior of Biomedical Materials*, *4*(7), 1504–1513. https://doi.org/10.1016/j.jmbbm.2011.05.020

Kraai, T., Brown, C., Neeff, M., & Fisher, K. (2011). Complications of bone-anchored hearing aids in pediatric patients. *International Journal of Pediatric Otorhinolaryngology*, *75*(6), 749–753. https://doi.org/10.1016/j.ijporl.2011.01.018

Kruyt, I. J., Banga, R., Banerjee, A., Mylanus, E. A. M., & Hol, M. K. S. (2018). Clinical evaluation of a new laser-ablated titanium implant for bone-anchored hearing in 34 patients: 1-year experience. *Clinical Otolaryngology*, *43*(2), 761–764. https://doi.org/10.1111/coa.13060

Kruyt, I. J., Nelissen, R. C., Johansson, M. L., Mylanus, E. A. M., & Hol, M. K. S. (2017). The IPS-scale: A new soft tissue assessment scale for percutaneous and transcutaneous implants for bone conduction devices. *Clinical Otolaryngology*, *42*(6), 1410–1413. https://doi.org/10.1111/coa.12922

Kwon, P. T., Rahman, S. S., Kim, D. M., Kopman, J. A., Karimbux, N. Y., & Fiorellini, J. P. (2005). Maintenance of osseointegration utilizing insulin therapy in a diabetic rat model. *Journal of Periodontology*, *76*(4), 621–626. https://doi.org/10.1902/jop.2005.76.4.621

Lanis, A., & Hultcrantz, M. (2013). Percutaneous osseointegrated implant surgery without skin thinning in children: A retrospective case review. *Otology & Neurotology*, *34*(4), 715–722. https://doi.org/10.1097/MAO.0b013e31827de4dd

Larsson, A., Tjellström, A., & Stalfors, J. (2015). Implant losses for the bone-anchored hearing devices are more frequent in some patients. *Otology & Neurotology*, *36*(2), 336–340. https://doi.org/10.1097/MAO.0000000000000446

Leterme, G., Bernardeschi, D., Bensemman, A., Coudert, C., Portal, J.-J., Ferrary, E., Sterkers, O., Vicaut, E., Frachet, B., & Bozorg Grayeli, A. (2015). Contralateral routing of signal hearing aid versus transcutaneous bone conduction in single-sided deafness. *Audiology & Neuro-Otology*, *20*(4), 251–260. https://doi.org/10.1159/000381329

Lillie, E. M., Urban, J. E., Lynch, S. K., Weaver, A. A., & Stitzel, J. D. (2016). Evaluation of skull cortical thickness changes with age and sex from computed tomography scans. *Journal of Bone and Mineral Research*, *31*(2), 299–307. https://doi.org/10.1002/jbmr.2613

Liu, Z., Aronson, J., Wahl, E. C., Liu, L., Perrien, D. S., Kern, P. A., Fowlkes, J. L., Thrailkill, K. M., Bunn, R. C., Cockrell, G. E., Skinner, R. A., & Lumpkin, C. K. (2007).

A novel rat model for the study of deficits in bone formation in type-2 diabetes. *Acta Orthopaedica*, *78*(1), 46–55. https://doi.org/10.1080/17453670610013411

Lloyd, S., Almeyda, J., Sirimanna, K. S., Albert, D. M., & Bailey, C. M. (2007). Updated surgical experience with bone-anchored hearing aids in children. *The Journal of Laryngology and Otology*, *121*(9), 826–831. https://doi.org/10.1017/S0022215107003714

Lukas, D., & Schulte, W. (1990). Periotest--a dynamic procedure for the diagnosis of the human periodontium. *Clinical Physics and Physiological Measurements*, *11*(1), 65–75. https://doi.org/10.1088/0143-0815/11/1/006

Lum, L. B., Beirne, O. R., & Curtis, D. A. (1991). Histologic evaluation of hydroxylapatite coated versus uncoated titanium blade implants in delayed and immediately loaded applications. *International Journal of Oral & Maxillofacial Implants*, *6*(4), 150–161.

Lustig, L. R., Arts, H. A., Brackmann, D. E., Francis, H. F., Molony, T., Megerian, C. A., Moore, G. F., Moore, K. M., Morrow, T., Potsic, W., Rubenstein, J. T., Srireddy, S., Syms, C. A., Takahashi, G., Vernick, D., Wackym, P. A., & Niparko, J. K. (2001). Hearing rehabilitation using the BAHA bone-anchored hearing aid: Results in 40 patients. *Otology & Neurotology*, *22*(3), 328–334. https://doi.org/10.1097/00129492-200105000-00010

Lynnerup, N., Astrup, J. G., & Sejrsen, B. (2005). Thickness of the human cranial diploe in relation to age, sex and general body build. *Head & Face Medicine*, *1*, 13. https://doi.org/10.1186/1746-160X-1-13

Magliulo, G., Turchetta, R., Iannella, G., Di Valperga Masino, R., Di Masino, R. V., & Vincentiis, M. de (2015). Sophono alpha system and subtotal petrosectomy with external

auditory canal blind sac closure. *European Archives of Oto-Rhino-Laryngology*, *272*(9), 2183–2190. https://doi.org/10.1007/s00405-014-3123-2

Mann, Z. F., & Kelley, M. W. (2011). Development of tonotopy in the auditory periphery. *Hearing Research*, *276*(1-2), 2–15. https://doi.org/10.1016/j.heares.2011.01.011

Marfatia, H., Priya, R., Sathe, N. U., & Mishra, S. (2016). Challenges during baha surgery: Our experience. *Indian Journal of Otolaryngology and Head and Neck Surgery*, *68*(3), 317–321. https://doi.org/10.1007/s12070-016-1002-4

Marieb, E. N., Mallatt, J., & Wilhelm, P. B. (2008). *Human anatomy*.

Marquezan, M., Osório, A., Sant'Anna, E., Souza, M. M., & Maia, L. (2012). Does bone mineral density influence the primary stability of dental implants? A systematic review. *Clinical Oral Implants Research*, *23*(7), 767–774. https://doi.org/10.1111/j.1600-0501.2011.02228.x

Marsella, P., Scorpecci, A., Pacifico, C., & Tieri, L. (2011). Bone-anchored hearing aid (baha) in patients with treacher collins syndrome: Tips and pitfalls. *International Journal of Pediatric Otorhinolaryngology*, *75*(10), 1308–1312. https://doi.org/10.1016/j.ijporl.2011.07.020

Marsella, P., Scorpecci, A., Vallarino, M. V., Di Fiore, S., & Pacifico, C. (2014). Sophono in pediatric patients: The experience of an italian tertiary care center. *Otolaryngology--Head and Neck Surgery*, *151*(2), 328–332. https://doi.org/10.1177/0194599814529925

Martínez, P., López, F., & Gómez, J. R. (2015). Cutaneous complications in osseointegrated implants: Comparison between classic and tissue preservation techniques. *Acta Otorrinolaringologica Espanola*, *66*(3), 148–153. https://doi.org/10.1016/j.otorri.2014.07.003

Mavrogenis, A. F., Dimitriou, R., Parvizi, J., & Babis, G. C. (2009). Biology of implant osseointegration. *Journal of Musculoskeletal & Neuronal Interactions*, *9*(2), 61–71.

McDermott, A.-L., & Sheehan, P. (2009). Bone anchored hearing aids in children. *Current Opinion in Otolaryngology & Head and Neck Surgery*, *17*(6), 488–493. https://doi.org/10.1097/MOO.0b013e32833237d7

McDermott, A.-L., Williams, J., Kuo, M. J., Reid, A. P., & Proops, D. W. (2008). The role of bone anchored hearing aids in children with down syndrome. *International Journal of Pediatric Otorhinolaryngology*, *72*(6), 751–757. https://doi.org/10.1016/j.ijporl.2008.01.035

McDermott, A.-L., Williams, J., Kuo, M., Reid, A., & Proops, D. (2009). The birmingham pediatric bone-anchored hearing aid program: A 15-year experience. *Otology & Neurotology*, *30*(2), 178–183. https://doi.org/10.1097/MAO.0b013e31818b6271

McKibbin, B. (1978). The biology of fracture healing in long bones. *The Journal of Bone and Joint Surgery. British Volume*, *60-B*(2), 150–162. https://doi.org/10.1302/0301-620X.60B2.350882

Medical, O. (n.d.). *How bone conduction systems work | Oticon Medical*. https://www.oticonmedical.com/bone-conduction/new-to-bone-conduction/what-is-bone-conduction/how-bone-conduction-systems-work

Meredith, N. (1998). Assessment of implant stability as a prognostic determinant. *The International Journal of Prosthodontics*, *11*(5), 491–501.

Meredith, N., Alleyne, D., & Cawley, P. (1996). Quantitative determination of the stability of the implant-tissue interface using resonance frequency analysis. *Clinical Oral Implants Research*, *7*(3), 261–267. https://doi.org/10.1034/j.1600-0501.1996.070308.x

Merheb, J., Temmerman, A., Rasmusson, L., Kübler, A., Thor, A., & Quirynen, M. (2016). Influence of skeletal and local bone density on dental implant stability in patients with osteoporosis. *Clinical Implant Dentistry and Related Research*, *18*(2), 253–260. https://doi.org/10.1111/cid.12290

Merheb, J., Vercruyssen, M., Coucke, W., & Quirynen, M. (2018). Relationship of implant stability and bone density derived from computerized tomography images. *Clinical Implant Dentistry and Related Research*, *20*(1), 50–57. https://doi.org/10.1111/cid.12579

Mohamad, S., Khan, I., Hey, S. Y., & Hussain, S. S. M. (2016). A systematic review on skin complications of bone-anchored hearing aids in relation to surgical techniques. *European Archives of Oto-Rhino-Laryngology*, *273*(3), 559–565. https://doi.org/10.1007/s00405-014-3436-1

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Journal of Clinical Epidemiology*, *62*(10), 1006–1012. https://doi.org/10.1016/j.jclinepi.2009.06.005

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Annals of Internal Medicine*, *151*(4), 264-9, W64. https://doi.org/10.7326/0003-4819-151-4-200908180-00135

Monksfield, P., Ho, E. C., Reid, A., & Proops, D. (2009). Experience with the longer (8.5 mm) abutment for bone-anchored hearing aid. *Otology & Neurotology*, *30*(3), 274–276. https://doi.org/10.1097/MAO.0b013e31819679ca

Mulvihill, D., Kumar, R., Muzaffar, J., Currier, G., Atkin, M., Esson, R., Limbrick, J., Gaskell, P., Banga, R., & Monksfield, P. (2019). Inter-rater reliability and validity of

holgers scores for the assessment of bone-anchored hearing implant images. *Otology & Neurotology*, *40*(2), 200–203. https://doi.org/10.1097/MAO.0000000000002100

Musiek, F. E., Weihing, J. A., & Oxholm, V. B. (2007). *Anatomy and physiology of the Central Auditory Nervous System: A Clinical Perspective*. Thieme.

Myers, E. N., Reyes, R. A., Tjellström, A., & Granström, G. (2000). Evaluation of implant losses and skin reactions around extraoral bone-anchored implants: A 0- to 8-year follow-up. *Otolaryngology–Head and Neck Surgery*, *122*(2), 272–276. https://doi.org/10.1016/S0194-5998(00)70255-5

Nalla, R. K., Kruzic, J. J., Kinney, J. H., & Ritchie, R. O. (2004). Effect of aging on the toughness of human cortical bone: Evaluation by r-curves. *Bone*, *35*(6), 1240–1246. https://doi.org/10.1016/j.bone.2004.07.016

Nazari, A., Bajaj, D., Zhang, D., Romberg, E., & Arola, D. (2009). Aging and the reduction in fracture toughness of human dentin. *Journal of the Mechanical Behavior of Biomedical Materials*, *2*(5), 550–559. https://doi.org/10.1016/j.jmbbm.2009.01.008

Nelissen, R. C., Agterberg, M. J. H., Hol, M. K. S., & Snik, A. F. M. (2016). Three-year experience with the sophono in children with congenital conductive unilateral hearing loss: Tolerability, audiometry, and sound localization compared to a bone-anchored hearing aid. *European Archives of Oto-Rhino-Laryngology*, *273*(10), 3149–3156. https://doi.org/10.1007/s00405-016-3908-6

Nelissen, R. C., Besten, C. A. den, Faber, H. T., Dun, C. A. J., Mylanus, E. A. M., & Hol, M. K. S. (2016). Loading of osseointegrated implants for bone conduction hearing at 3 weeks: 3-year stability, survival, and tolerability. *European Archives of Oto-Rhino-Laryngology*, *273*(7), 1731–1737. https://doi.org/10.1007/s00405-015-3746-y

Nelissen, R. C., Stalfors, J., Wolf, M. J. F. de, Flynn, M. C., Wigren, S., Eeg-Olofsson, M., Green, K., Rothera, M. P., Mylanus, E. A. M., & Hol, M. K. S. (2014). Long-term stability, survival, and tolerability of a novel osseointegrated implant for bone conduction hearing: 3-year data from a multicenter, randomized, controlled, clinical investigation. *Otology & Neurotology*, *35*(8), 1486–1491. https://doi.org/10.1097/MAO.0000000000000533

Nelissen, R. C., Wigren, S., Flynn, M. C., Meijer, G. J., Mylanus, E. A. M., & Hol, M. K. S. (2015). Application and interpretation of resonance frequency analysis in auditory osseointegrated implants: A review of literature and establishment of practical recommendations. *Otology & Neurotology*, *36*(9), 1518–1524. https://doi.org/10.1097/MAO.0000000000000833

Nelson, K. L., Cox, M. D., Richter, G. T., & Dornhoffer, J. L. (2016). A comparative review of osseointegration failure between osseointegrated bone conduction device models in pediatric patients. *Otology & Neurotology*, *37*(3), 276–280. https://doi.org/10.1097/MAO.0000000000000970

O'Niel, M. B., Runge, C. L., Friedland, D. R., & Kerschner, J. E. (2014). Patient outcomes in magnet-based implantable auditory assist devices. *JAMA Otolaryngology-- Head & Neck Surgery*, *140*(6), 513–520. https://doi.org/10.1001/jamaoto.2014.484

Organization, W. H. (2020). *Deafness and hearing loss*. https://www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss

Parithimarkalaignan, S., & Padmanabhan, T. V. (2013). Osseointegration: An update. *Journal of Indian Prosthodontic Society*, *13*(1), 2–6. https://doi.org/10.1007/s13191-013-0252-z

Paul, P. V., & Whitelaw, G. M. (2010). *Hearing and deafness, 308*. Jones & Bartlett Publishers.

Pilliar, R. M., LEE, J. M., & MANIATOPOULOS, C. (1986). Observations on the effect of movement on bone ingrowth into porous-surfaced implants. *Clinical Orthopaedics and Related Research*, *&NA;*(208), 108???113. https://doi.org/10.1097/00003086-198607000-00023

Powell, H. R. F., Rolfe, A. M., & Birman, C. S. (2015). A comparative study of audiologic outcomes for two transcutaneous bone-anchored hearing devices. *Otology & Neurotology*, *36*(9), 1525–1531. https://doi.org/10.1097/MAO.0000000000000842

Proops, D. W. (1996). The birmingham bone anchored hearing aid programme: Surgical methods and complications. *The Journal of Laryngology and Otology. Supplement*, *21*, 7–12. https://doi.org/10.1017/S0022215100136217

Raphael, Y., & Altschuler, R. A. (2003). Structure and innervation of the cochlea. *Brain Research Bulletin*, *60*(5-6), 397–422. https://doi.org/10.1016/S0361-9230(03)00047-9

Razi, H., Birkhold, A. I., Weinkamer, R., Duda, G. N., Willie, B. M., & Checa, S. (2015). Aging leads to a dysregulation in mechanically driven bone formation and resorption. *Journal of Bone and Mineral Research*, *30*(10), 1864–1873. https://doi.org/10.1002/jbmr.2528

Reinfeldt, S., Håkansson, B., Taghavi, H., & Eeg-Olofsson, M. (2015). New developments in bone-conduction hearing implants: A review. *Medical Devices (Auckland, N.Z.)*, *8*, 79–93. https://doi.org/10.2147/MDER.S39691

Reinfeldt, S., Håkansson, B., Taghavi, H., Fredén Jansson, K.-J., & Eeg-Olofsson, M. (2015). The bone conduction implant: Clinical results of the first six patients. *International Journal of Audiology*, *54*(6), 408–416. https://doi.org/10.3109/14992027.2014.996826

Retzepi, M., & Donos, N. (2010). The effect of diabetes mellitus on osseous healing. *Clinical Oral Implants Research*, *21*(7), 673–681. https://doi.org/10.1111/j.1600-0501.2010.01923.x

Richman, J., Makrides, L., & Prince, B. (1980). Research methodology and applied statistics. *Physiother Can*, *32*, 253–257.

Roman, S., Nicollas, R., & Triglia, J.-M. (2011). Practice guidelines for bone-anchored hearing aids in children. *European Annals of Otorhinolaryngology, Head and Neck Diseases*, *128*(5), 253–258. https://doi.org/10.1016/j.anorl.2011.04.005

Rosato, M. T., Schneider, S. H., & Shapses, S. A. (1998). Bone turnover and insulin-like growth factor I levels increase after improved glycemic control in noninsulin-dependent diabetes mellitus. *Calcified Tissue International*, *63*(2), 107–111. https://doi.org/10.1007/s002239900498

Salvi, R., Sun, W., & Lobarinas, E. (2007). *Anatomy and physiology of the peripheral auditory system*. Thieme.

Samra, B. (2018, April). Bone Anchored Hearing Systems - Principles and Candidacy Barinder Samra. *Audiology Online*. https://www.audiologyonline.com/articles/bone-anchored-hearing-systems-principles-22366

Sardiwalla, Y., Jufas, N., & Morris, D. P. (2017). Direct cost comparison of minimally invasive punch technique versus traditional approaches for percutaneous bone anchored hearing devices. *Journal of Otolaryngology - Head & Neck Surgery*, *46*(1), 46. https://doi.org/10.1186/s40463-017-0222-2

Savage, J. H., & Frawley, T. (2019). Tullamore classification: Pbahs fixture site reaction reevaluation. In *7th International Congress on Bone Conduction Hearing and Related Technologies.*

Sayardoust, S., Omar, O., & Thomsen, P. (2017). Gene expression in peri-implant crevicular fluid of smokers and nonsmokers. 1. The early phase of osseointegration. *Clinical Implant Dentistry and Related Research*, *19*(4), 681–693. https://doi.org/10.1111/cid.12486

Sayardoust, S., Omar, O., Norderyd, O., & Thomsen, P. (2018). Implant-associated gene expression in the jaw bone of smokers and nonsmokers: A human study using quantitative qPCR. *Clinical Oral Implants Research*, *29*(9), 937–953. https://doi.org/10.1111/clr.13351

Schatzker, J., Horne, J. G., & Sumner-Smith, G. (1975). The effect of movement on the holding power of screws in bone. *Clinical Orthopaedics and Related Research*(111), 257–262. https://doi.org/10.1097/00003086-197509000-00032

Sclar, A. G. (2007). Guidelines for flapless surgery. *Journal of Oral and Maxillofacial Surgery*, *65*(7 Suppl 1), 20–32. https://doi.org/10.1016/j.joms.2007.03.017

Sennerby, L., & Meredith, N. (2008). Implant stability measurements using resonance frequency analysis: Biological and biomechanical aspects and clinical implications. *Periodontology 2000*, *47*, 51–66. https://doi.org/10.1111/j.1600-0757.2008.00267.x

Shah, F. A., Johansson, M. L., Omar, O., Simonsson, H., Palmquist, A., & Thomsen, P. (2016). Laser-modified surface enhances osseointegration and biomechanical anchorage of commercially pure titanium implants for bone-anchored hearing systems. *PloS One*, *11*(6), e0157504. https://doi.org/10.1371/journal.pone.0157504

Shapiro, S., Ramadan, J., & Cassis, A. (2018). BAHA skin complications in the pediatric population: Systematic review with meta-analysis. *Otology & Neurotology*, *39*(7), 865–873. https://doi.org/10.1097/MAO.0000000000001877

Shin, J.-W., Kim, S. H., Choi, J. Y., Park, H.-J., Lee, S.-C., Choi, J.-S., Park, H. Q., & Lee, H.-K. (2016). Surgical and audiologic comparison between sophono and bone-anchored hearing aids implantation. *Clinical and Experimental Otorhinolaryngology*, *9*(1), 21–26. https://doi.org/10.21053/ceo.2016.9.1.21

Shrout, P. E., & Fleiss, J. L. (1979). Intraclass correlations: Uses in assessing rater reliability. *Psychological Bulletin*, *86*(2), 420–428. https://doi.org/10.1037/0033-2909.86.2.420

Siegert, R. (2011). Partially implantable bone conduction hearing aids without a percutaneous abutment (otomag): Technique and preliminary clinical results. *Advances in Oto-Rhino-Laryngology*, *71*, 41–46. https://doi.org/10.1159/000323720

Siegert, R., & Kanderske, J. (2013). A new semi-implantable transcutaneous bone conduction device: Clinical, surgical, and audiologic outcomes in patients with congenital ear canal atresia. *Otology & Neurotology*, *34*(5), 927–934. https://doi.org/10.1097/MAO.0b013e31828682e5

Singam, S., Williams, R., Saxby, C., & Houlihan, F. P. (2014). Percutaneous bone-anchored hearing implant surgery without soft-tissue reduction: Up to 42 months of follow-up. *Otology & Neurotology*, *35*(9), 1596–1600. https://doi.org/10.1097/MAO.0000000000000522

Singer, A. J., & Clark, R.A. (1999) Cutaneous wound healing. *New England Journal of Medicine, 341*(10)*,* 738–746.

Singh, J. A., Schleck, C., Harmsen, W. S., Jacob, A. K., Warner, D. O., & Lewallen, D. G. (2015). Current tobacco use is associated with higher rates of implant revision and deep infection after total hip or knee arthroplasty: A prospective cohort study. *BMC Medicine*, *13*, 283. https://doi.org/10.1186/s12916-015-0523-0

Siqueira, J. T., Cavalher-Machado, S. C., Arana-Chavez, V. E., & Sannomiya, P. (2003). Bone formation around titanium implants in the rat tibia: Role of insulin. *Implant Dentistry*, *12*(3), 242–251. https://doi.org/10.1097/01.ID.0000074440.04609.4F

Snik, A. F. M., Mylanus, E. A. M., Proops, D. W., Wolfaardt, J. F., Hodgetts, W. E., Somers, T., Niparko, J. K., Wazen, J. J., Sterkers, O., Cremers, C. W. R. J., & Tjellström, A. (2005). Consensus statements on the BAHA system: Where do we stand at present? *The Annals of Otology, Rhinology & Laryngology. Supplement*, *195*, 2–12. https://doi.org/10.1177/00034894051145S1201

Søballe, K., Hansen, E. S., B-Rasmussen, H., Jørgensen, P. H., & Bünger, C. (1992). Tissue ingrowth into titanium and hydroxyapatite-coated implants during stable and unstable mechanical conditions. *Journal of Orthopaedic Research*, *10*(2), 285–299. https://doi.org/10.1002/jor.1100100216

Sprinzl, G., Lenarz, T., Ernst, A., Hagen, R., Wolf-Magele, A., Mojallal, H., Todt, I., Mlynski, R., & Wolframm, M. D. (2013). First European multicenter results with a new transcutaneous bone conduction hearing implant system: Short-term safety and efficacy. *Otology & Neurotology*, *34*(6), 1076–1083. https://doi.org/10.1097/MAO.0b013e31828bb541

Srinivasan, S., Gross, T. S., & Bain, S. D. (2012). Bone mechanotransduction May require augmentation in order to strengthen the senescent skeleton. *Ageing Research Reviews*, *11*(3), 353–360. https://doi.org/10.1016/j.arr.2011.12.007

Stewart, C. M., Clark, J. H., & Niparko, J. K. (2011). Bone-anchored devices in single-sided deafness. *Advances in Oto-Rhino-Laryngology*, *71*, 92–102. https://doi.org/10.1159/000323589

Street, J., Bao, M., deGuzman, L., Bunting, S., Peale, F. V., Ferrara, N., Steinmetz, H., Hoeffel, J., Cleland, J. L., Daugherty, A., van Bruggen, N., Redmond, H. P., Carano, R. A. D., & Filvaroff, E. H. (2002). Vascular endothelial growth factor stimulates bone repair by promoting angiogenesis and bone turnover. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(15), 9656–9661. https://doi.org/10.1073/pnas.152324099

Sylvester, D. C., Gardner, R., Reilly, P. G., Rankin, K., & Raine, C. H. (2013). Audiologic and surgical outcomes of a novel, nonpercutaneous, bone conducting hearing implant. *Otology & Neurotology*, *34*(5), 922–926. https://doi.org/10.1097/MAO.0b013e31827e60bd

Szmukler-Moncler, S., Salama, H., Reingewirtz, Y., & Dubruille, J. H. (1998). Timing of loading and effect of micromotion on bone-dental implant interface: Review of experimental literature. *Journal of Biomedical Materials Research*, *43*(2), 192–203. https://doi.org/10.1002/(SICI)1097-4636(199822)43:2<192::AID-JBM14>3.0.CO;2-K

Takahashi, K., Morita, Y., Ohshima, S., Izumi, S., Kubota, Y., & Horii, A. (2017). Bone density development of the temporal bone assessed by computed tomography. *Otology & Neurotology*, *38*(10), 1445–1449. https://doi.org/10.1097/MAO.0000000000001566

Takizawa, M., Suzuki, K., Matsubayashi, T., Kikuyama, M., Suzuki, H., Takahashi, K., Katsuta, H., Mitsuhashi, J., Nishida, S., Yamaguchi, S., Yoshimoto, K., Itagaki, E., & Ishida, H. (2008). Increased bone resorption May play a crucial role in the occurrence of osteopenia in patients with type 2 diabetes: Possible involvement of accelerated polyol pathway in its pathogenesis. *Diabetes Research and Clinical Practice*, *82*(1), 119–126. https://doi.org/10.1016/j.diabres.2008.07.008

Tietze, L., & Papsin, B. (2001). Utilization of bone-anchored hearing aids in children. *International Journal of Pediatric Otorhinolaryngology*, *58*(1), 75–80. https://doi.org/10.1016/S0165-5876(00)00472-9

Tjellström, A., & Granström, G. (1994). Long-term follow-up with the bone-anchored hearing aid: A review of the first 100 patients between 1977 and 1985. *Ear, Nose & Throat Journal*, *73*(2), 112–114. https://doi.org/10.1177/014556139407300210

Tjellström, A., & Granström, G. (1995). One-stage procedure to establish osseointegration: A zero to five years follow-up report. *The Journal of Laryngology and Otology*, *109*(7), 593–598. https://doi.org/10.1017/S0022215100130816

Tjellström, A., Granström, G., & Odersjö, M. (2007). Survival rate of self-tapping implants for bone-anchored hearing aids. *The Journal of Laryngology and Otology*, *121*(2), 101–104. https://doi.org/10.1017/S002221510600243X

Tjellström, A., Håkansson, B. O., & Granström, G. (2001). Bone-anchored hearing aids. *Otolaryngologic Clinics of North America*, *34*(2), 337–364. https://doi.org/10.1016/S0030-6665(05)70335-2

Tjellström, A., Lindström, J., Hallén, O., Albrektsson, T., & Brånemark, P. I. (1981). Osseointegrated titanium implants in the temporal bone. A clinical study on bone-anchored hearing aids. *The American Journal of Otology*, *2*(4), 304.

Tjellström, A., Rosenhall, U., Lindström, J., Hallén, O., Albrektsson, T., & Brånemark, P. I. (1983). Five-year experience with skin-penetrating bone-anchored implants in the temporal bone. *Acta Oto-Laryngologica*, *95*(5-6), 568–575. https://doi.org/10.3109/00016488309139444

Tomlinson, A. R., Hudson, M. L., Horn, K. L., Bell, E. M., Petersen, T. R., & Kraai, T. L. (2017). Pediatric calvarial bone thickness in patients with and without aural atresia. *Otology & Neurotology*, *38*(10), 1470–1475. https://doi.org/10.1097/MAO.0000000000001579

Uhthoff, H. K. (1973). MECHANICAL FACTORS INFLUENCING THE HOLDING POWER of SCREWS in COMPACT BONE. *The Journal of Bone and Joint Surgery. British Volume*, *55-B*(3), 633–639. https://doi.org/10.1302/0301-620X.55B3.633

van de Berg, R., Stokroos, R. J., Hof, J. R., & Chenault, M. N. (2010). Bone-anchored hearing aid: A comparison of surgical techniques. *Otology & Neurotology*, *31*(1), 129–135. https://doi.org/10.1097/MAO.0b013e3181c29fec

van der Pouw, C. T., Mylanus, E. A., & Cremers, C. W. (1999). Percutaneous implants in the temporal bone for securing a bone conductor: Surgical methods and results. *The Annals of Otology, Rhinology, and Laryngology*, *108*(6), 532–536. https://doi.org/10.1177/000348949910800602

Verheij, E., Bezdjian, A., Grolman, W., & Thomeer, H. G. X. M. (2016). A systematic review on complications of tissue preservation surgical techniques in percutaneous bone conduction

hearing devices. *Otology & Neurotology*, *37*(7), 829–837. https://doi.org/10.1097/MAO.0000000000001091

Wallberg, E., Granström, G., Tjellström, A., & Stalfors, J. (2011). Implant survival rate in bone-anchored hearing aid users: Long-term results. *The Journal of Laryngology and Otology*, *125*(11), 1131–1135. https://doi.org/10.1017/S0022215111001447

Wang, F., Song, Y., Li, D., Li, C., Wang, Y., Zhang, N., & Wang, B. (2010). Type 2 diabetes mellitus impairs bone healing of dental implants in gk rats. *Diabetes Research and Clinical Practice*, *88*(1), e7-9. https://doi.org/10.1016/j.diabres.2010.01.017

Wang, Y., Zhang, Y., & Miron, R. J. (2016). Health, maintenance, and recovery of soft tissues around implants. *Clinical Implant Dentistry and Related Research*, *18*(3), 618–634. https://doi.org/10.1111/cid.12343

Ward, K. D., & Klesges, R. C. (2001). A meta-analysis of the effects of cigarette smoking on bone mineral density. *Calcified Tissue International*, *68*(5), 259–270. https://doi.org/10.1007/BF02390832

Wazen, J. J., Young, D. L., Farrugia, M. C., Chandrasekhar, S. S., Ghossaini, S. N., Borik, J., Soneru, C., & Spitzer, J. B. (2008). Successes and complications of the baha system. *Otology & Neurotology*, *29*(8), 1115–1119. https://doi.org/10.1097/MAO.0b013e318187e186

Westover, L., Faulkner, G., Hodgetts, W., & Raboud, D. (2016). Advanced system for implant stability testing (ASIST). *Journal of Biomechanics*, *49*(15), 3651–3659. https://doi.org/10.1016/j.jbiomech.2016.09.043

Wilkie, M. D., Chakravarthy, K. M., Mamais, C., & Temple, R. H. (2014). Osseointegrated hearing implant surgery using a novel hydroxyapatite-coated concave abutment design.

Otolaryngology--Head and Neck Surgery, *151*(6), 1014–1019. https://doi.org/10.1177/0194599814551150

Willie, B. M., Yang, X., Kelly, N. H., Han, J., Nair, T., Wright, T. M., van der Meulen, M. C. H., & Bostrom, M. P. G. (2010). Cancellous bone osseointegration is enhanced by in vivo loading. *Tissue Engineering. Part C, Methods*, *16*(6), 1399–1406. https://doi.org/10.1089/ten.tec.2009.0776

Wilson, D. F., & Kim, H. H. (2013). A minimally invasive technique for the implantation of bone-anchored hearing devices. *Otolaryngology--Head and Neck Surgery*, *149*(3), 473–477. https://doi.org/10.1177/0194599813492946

Wood, M. R., & Vermilyea, S. G. (2004). A review of selected dental literature on evidence-based treatment planning for dental implants: Report of the committee on research in fixed prosthodontics of the academy of fixed prosthodontics. *The Journal of Prosthetic Dentistry*, *92*(5), 447–462. https://doi.org/10.1016/j.prosdent.2004.08.003

Zimmermann, E. A., Launey, M. E., & Ritchie, R. O. (2010). The significance of crack-resistance curves to the mixed-mode fracture toughness of human cortical bone. *Biomaterials*, *31*(20), 5297–5305. https://doi.org/10.1016/j.biomaterials.2010.03.056

Appendix

Ethics approvals and relevant documentation of projects included in this thesis

Centre universitaire de santé McGill | McGill University Health Centre

2018-07-20

Dr. Sam Daniel
Otorhinolaryngology (Pediatric)

c/o: Aren Bezdjian
email: aren.bezdjian@mail.mcgill.ca

RE: Final REB Approval of a New Research Project
Assessing skin tolerability of percutaneous Bone Anchored Hearing Implants (BAHI) using the Holger's classification, the IPS and Tullamore scales
(BAHA skin reaction scales / 2019-4776)

MUHC REB Co-Chair for the CTGQ panel: Me Marie Hirtle

Dear Dr. Daniel,

Thank you for the initial submission of the research project indicated above.

On 2018-07-20, a delegated review of the research project was provided by member(s) of the McGill University Health Centre (MUHC) Research Ethics Board (REB), more precisely its Cells, Tissues, Genetics & Qualitative research (CTGQ) panel. The research project was found to meet scientific and ethical standards for conduct at the MUHC.

The following documents were approved or acknowledged by the MUHC REB:

- Initial Submission Form (F11NIR - 33215)
- Research protocol
  - (Research proposal - skin tolerability scales V2.docx) [Date: 2018-06-29, Version: 2]
- Information & consent form
  - (information letter.docx) [Date: 2018-06-29, Version: V1]
- Questionnaires & research material (Survey.docx)
  - [Date: 2018-06-22, Version: 1]

This will be reported to the MUHC REB and will be entered accordingly into the minutes of the next CTGQ meeting. Please be advised that you may only initiate the research project after all required reviews and decisions are received and documented and you have received the MUHC authorization letter.

The approval of the research project is valid until 2019-07-20.

All research involving human subjects requires review at recurring intervals. To comply with the regulation for continuing review of at least once per year, it is the responsibility of the investigator to submit an *Annual Renewal Submission Form* (F9) to the REB prior to expiry. Please be advised that should be protocol reach its expiry before a Continuing

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2017-08-02

Dr. Sam Daniel
Pediatric Otolaryngology
MUHC - Montreal Children's Hospital
1001 boul. Decarie
Montreal QC H4A 3J1

email: aren.bezdjian@mail.mcgill.ca

Re: MUHC Authorization 2018-3444
Factors influencing osseointegration of bone anchored hearing implants; a retrospective cohort study **(Osseointegration failure cohort study)**

Dear Dr. Daniel,

We are writing to confirm that the study mentioned above has received all required institutional approvals.

You are hereby authorized to conduct your research at the McGill University Health Centre (MUHC) as well as to initiate recruitment.

Please refer to the MUHC Study number in all future correspondence relating to this study.

In accordance with applicable policies it is the investigator's responsibility to ensure that staff involved in the study is competent and qualified and, when required, has received certification to conduct clinical research.

Should you have any questions, please do not hesitate to contact the support for the Personne mandatée at personne.mandatee@muhc.mcgill.ca.

We wish you every success with the conduct of the research.

Sincerely,

Sheldon Levy

Sheldon Levy
for:
Marie Hirtle, LL.B. LL.M.
Personne Mandatée
Centre Universitaire de Santé McGill

Centre universitaire de santé McGill | McGill University Health Centre

2020-03-23

Dr. Sam Daniel
Pediatric ENT
MUHC
email: aren.bezdjian@mail.mcgill.ca

RE: REB Conditional Approval of a New Research Project
Evaluation of peri-operative outcomes of bone conduction hearing implants in pediatric and adult patients; retrospective cohort series **(Bone conduction hearing implant retrospective studies / 2020-5733)**

MUHC REB Co-Chair for the PED panel: M. Vincent Lajoie

Dear Dr. Daniel,

Thank you for the initial submission of the research project indicated above.

On 2020-03-23, a delegated review of the research project was provided by member(s) of the McGill University Health Centre (MUHC) Research Ethics Board (REB), more precisely its Pediatric (PED) panel.

The *Initial Submission Form* (F11HRR-45019) as well as the following documents were reviewed:

- **Research protocol**
- Study protocol BAHA 23092019.doc, [Date: 2019-09-26, Version: 1]
- **Other REBs involved**
- Final Authorization-Single Site.pdf, [Date: 2017-08-02]
- **signed commitment**
- PI Commitment and Signature_2016-03-30.docx

After reviewing the documents, **this research project was approved unanimously by the MUHC REB conditional upon the receipt of responses to the conditions listed in the *REB Conditions & PI Responses Form* (F20-56750) and documents attached to it.** This will be reported to the MUHC REB and will be entered accordingly into the minutes of the next PED meeting.

Corrected documents attached to the F20-56750 will have to be submitted in "track changes".

We trust this will prove satisfactory to you. Thank you for your consideration in this matter.

Best Regards,

August 28, 2018

Dear colleagues,

Information Letter for Survey Research

Skin reactions following percutaneous bone anchored hearing implant placement is not uncommon. Currently, skin tolerability is assessed by the Holgers classification. Reports mention that this classification is outdated. In our practice at the MUHC, we have often observed discrepancies amongst scorers of skin reactions with this classification scale. Two new scales have emerged.

The aim of the present survey is to help contribute new knowledge in this specific complication seen in otolaryngology practice. We seek to find out which scale has less variability amongst scorers. It is expected that the data will be published in a peer-reviewed otolaryngology journal.

We would greatly appreciate if you could complete the brief 4-item questionnaire below, followed by 36 evaluations using three available skin tolerability scales for bone anchored hearing implants. The survey and evaluation should take approximately 20 minutes of your time.

There are no known or anticipated risks from participating in this study.

All information that you provide will remain confidential and anonymous.

By completing the survey you are giving consent for your anonymous responses to be included in the study. If you have any questions please feel free to contact me by email at: (sam.daniel@mcgill.ca).

Thank you for your participation.

Sincerely,

Sam J Daniel, MD, FRCSC
Professor, Pediatric Surgery and Otolaryngology, McGill University
Associate Chair, Department of Pediatric Surgery
Director Pediatric Otolaryngology, Montreal Children's Hospital

McGill University Health Centre – Glen Site
Montreal Children's Hospital
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Version 1.0
June 22, 2018

SURVEY FOR OTOLARYNGOLOGISTS AND HEALTH PROFESSIONALS
Assessing skin tolerability of percutaneous Bone Anchored Hearing Implants (BAHI) using the Holger's classification, the IPS and Tullamore scales

The survey contains 4 questions and will take less than 3 minutes to complete.

Characteristics and experience of the respondent

1) Years of practice as ENT

- ☐ < 5 years -
- ☐ 5-10 years
- ☐ 10-20 years
- ☐ 20-30 years
- ☐ > 30 years

2) Predominant population

- ☐ Pediatric
- ☐ Adult

3) Approximately how many percutaneous BAHA surgeries do you perform per month or year?

- _____

4) Have you ever used a skin tolerability scale (i.e. Holgers) to assess skin reactions after percutaneous BAHA surgery?

- ☐ Yes
- ☐ No

If so, which scale?:

Thank you very much for your collaboration!

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2017-06-15

Dr. Sam Daniel
Peduiatric Otolaryngology
MUHC - Montreal Chidlren's Hospital
101 boul. Decarie,
Montreal, QC H4A 3J1

email: aren.bezdjian@mail.mcgill.ca

RE: REB Conditional Approval of a New Research Project
Factors influencing osseointegration of bone anchored hearing implants; a retrospective cohort study **(Osseointegration failure cohort study / 2018-3444)**
MUHC REB Co-Chair for the PED panel: Ms. Lori Seller

Dear Dr. Daniel,

Thank you for the initial submission of the research project indicated above.

On 2017-06-15, a delegated review of the research project was provided by member(s) of the McGill University Health Centre (MUHC) Research Ethics Board (REB), more precisely its pediatric panel (PED).

The *Initial Submission Form* (F11HRR-16706) as well as the following documents were reviewed:

- Research Proposal, Date: 2017-06-05, Version: 3
- Data extraction sheet,

After reviewing the documents, **this research project was approved unanimously by the MUHC REB conditional upon the receipt of responses to the conditions listed in the *REB Conditions & PI Responses Form* (F20-19713) and documents attached to it.** This will be reported to the MUHC REB and will be entered accordingly into the minutes of the next PED meeting.

Corrected documents attached to the F20-19713 will have to be submitted in “track changes”.

We trust this will prove satisfactory to you. Thank you for your consideration in this matter.

Best Regards,

Centre universitaire de santé McGill | McGill University Health Centre

2018-07-20

Dr. Sam Daniel
1001 Decarie Boulevard
Room A02.3017
Montreal, Quebec
H4A 3J1

c/o: Aren Bezdjian

email: aren.bezdjian@mail.mcgill.ca

Re: MUHC Authorization (BAHA skin reaction scales / 2019-4776)

"Assessing skin tolerability of percutaneous Bone Anchored Hearing Implants (BAHI) using the Holger's classification, the IPS and Tullamore scales"

Dear Dr. Daniel,

We are writing to confirm that the study mentioned above has received research ethics board approval and all required institutional approvals.

You are hereby authorized to conduct your research at the McGill University Health Centre (MUHC) as well as to initiate recruitment.

Please refer to the MUHC Study number in all future correspondence relating to this study.

In accordance with applicable policies it is the investigator's responsibility to ensure that staff involved in the study is competent and qualified and, when required, has received certification to conduct clinical research.

Should you have any questions, please do not hesitate to contact the support for the Personne mandatée at personne.mandatee@muhc.mcgill.ca.

We wish you every success with the conduct of the research.

Sincerely,

Sheldon Levy

Sheldon Levy
for:
Marie Hirtle, LL.B. LL.M.
Personne Mandatée
Centre Universitaire de Santé McGill

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Tél/Tel: (514) 398-3124

10 November 2020

Dr. Bettina Willie
Division of Pediatric Surgery
Shriners Hospitals for Children
1003 Decarie Boulevard
Montreal QC H4A 0A9

RE: IRB Study Number A08-M31-18B
Comparison of noninvasive and conventional methods to measure primary stability of bone anchored hearing devices implanted in human temporal bones and artificial Sawbone

Dear Dr. Willie,

On 09 November 2020, at a meeting of the Institutional Review Board, the following amendment received a full Board review and approval:

- Amendment Notification (dated 30 October 2020) and Amended Study Protocol, version September 14, 2020 (amended October 29, 2020)
- English and French Pediatric Research Information and Consent Form, version September 14, 2020 (amended October 2020).

The Investigators are reminded of the requirement to report all McGill IRB approved study documents to the Research Ethics Offices (REOs) of participating study sites, if applicable. Please contact the individual REOs for instructions on how to proceed. Research funds may be withheld and/or the study's data may be revoked if there is a failure to comply with this requirement.

Sincerely,

Roberta M. Palmour

Roberta Palmour, PhD
Chair
Institutional Review Board

Cc: A08-M31-18B