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# Three-year Outcomes of a Randomized Controlled Trial Comparing a 4.5-mm-Wide to a 3.75-mm-Wide Titanium Implant for Bone Conduction Hearing

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**Objective:** To compare 3-year implant stability, survival, and tolerability of a 4.5-mm-wide (test) and a 3.75-mm-wide (control) percutaneous titanium implant for bone-conduction hearing, loaded with the sound processor after 3 weeks.

**Methods:** Sixty implants were allocated in a 2:1 ratio (test-control) in 57 adult patients included in this prospective randomized controlled clinical trial. Follow-up visits were performed at 7, 14, 21, and 28 days; 6 and 12 weeks; 6 months; and at 1, 2, and 3 years after implantation. During these visits, the implant stability quotient (ISQ) was measured by means of resonance frequency analysis (RFA). The peri-abutment soft tissue status was assessed according to the Holgers classification. Skin height around the abutment was evaluated.

**Results:** The mean area-under-the-curve (AUC) of ISQ-low was statistically significantly higher for the test implant (65.7 versus 61.4,  $p=0.0002$ ). Both implants showed high survival rates (97.4% versus 95.0%,  $p=0.6374$ ). Adverse

soft tissue reactions were observed sporadically, with no significant inter-group differences. Skin thickening was seen in the majority of the patients, but no correlation with adverse soft tissue reactions or implant type was observed.

**Conclusion:** The 4.5-mm-wide implant provides significantly higher ISQ values during the first 3 years after surgery compared with the previous generation 3.75-mm-wide implant. Both implants showed high survival rates and good tolerability. These long-term results indicate that the wider implant, loaded with a sound processor at 3 weeks, is a safe and well-performing option for hearing rehabilitation in specific types of hearing loss. **Key Words:** Bone-anchored hearing aid—Bone-anchored hearing—Hearing loss—Holgers—Implant loss—Implant stability quotient—Implant stability—Soft tissue reactions—Wide-diameter implant.

*Otol Neurotol* 39:609–615, 2018.

Since its introduction in 1977 (1), the most frequently observed complications of percutaneous titanium implants for bone-conduction hearing are implant loss (1.6–17.4%) and adverse soft tissue reactions (2.4–38.1%) (2,3). Over the years, modifications in surgical

technique and implant design have been made, aiming to reduce these complications (4–7).

Based on improved outcomes of wider titanium implants seen in dental research (8), the design of titanium implants for bone-conduction devices has been modified as well. These wider implants have a diameter of 4.5 mm compared with the 3.75 mm wide previous generation implants. This increase results in an enlarged contact area between implant and bone, resulting in a higher implant stability quotient (ISQ) (9,10). It was also advocated that higher levels of initial stability allow for earlier loading of the implant with the sound processor, hence, starting hearing rehabilitation quicker. Loading titanium implants 3 weeks after surgery has been reported to be safe (10–13).

The current randomized controlled clinical trial (RCT) investigated the 3-year outcomes of a 4.5-mm-wide (test) implant in comparison to the previous generation 3.75-mm-wide (control) implant on longer-term implant survival, ISQ, and soft tissue tolerability. This study is a continuation of the previously published study that presented clinical results with a follow-up period of 6 months

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Funding: Oticon Medical AB (Askim, Sweden) acted as sponsor and provided financial support for this study.

The authors report financial support to the authors' institution (Radboudumc) for conducting clinical studies from Oticon Medical AB (Askim, Sweden) and from Cochlear Bone Anchored Solutions AB (Mölnlycke, Sweden), also outside the submitted work. The authors declare that they have no other conflict of interest.

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DOI: 10.1097/MAO.0000000000001761

(11,14). We studied the intra-subject ISQ-trends to gain additional understanding of how implant stability evolves over time. Finally, we assessed the long-term safety of loading both test and control implants at 3 weeks after implantation.

## MATERIALS AND METHODS

### Patients and Implants

Patients, indicated for a percutaneous bone-conduction device in our tertiary referral center, had to be at least 18 years of age, to have a bone thickness of at least 4 mm at the implant site, and to provide written informed consent to be eligible for inclusion. Exclusion criteria were as follows: a more than 6 mm abutment needed; the inability to participate in follow-up visits or presumed doubt, for any reason, that the patient would not be able to attend all follow-up visits; a history of psychiatric diseases or mental disabilities; and the presence of diseases or a history of treatments known to compromise bone quality at the implant site (e.g., radiation therapy, osteoporosis, diabetes mellitus).

The test implant was the Wide Ponto implant (diameter 4.5 mm, length 4 mm) with a 6 mm abutment, and the control implant was the previous generation Ponto implant (diameter 3.75 mm, length 4 mm) with an identical 6 mm abutment. All implants and abutments are manufactured by Oticon Medical AB (Askim, Sweden).

The current study was performed in accordance with the guidelines established in the Declaration of Helsinki (Washington 2002), ISO 14155, Good Clinical Practice (International Conference on Harmonization Good Clinical Practice), and was approved by the local ethical committee (registration number 2011/497; NL nr.38556.091.11).

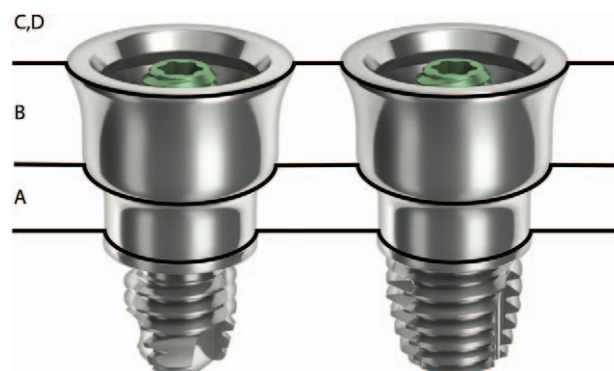
### Study Design

The primary objective of this RCT was to demonstrate superiority in implant stability, measured in ISQ-low values, of the test implant compared with the control implant during 3-year follow-up.

The secondary objectives were to observe trends in ISQ over all visits and to compare ISQ-high values, implant survival, postoperative complications, and soft tissue tolerability.

A power calculation was conducted to determine the sample size based on the primary outcome parameter (11). Based on data from a similarly designed study (15), an expected difference of 4.5 in the mean area under the curve (AUC) of the ISQ-low values of the test and the control groups, with unequal standard deviations [SDs] of 2.8 and 5.5, respectively, were used to determine the sample size. Due to unequal variance in the SDs, a two-sided *t* test with Satterthwaite's correction was performed. With a randomized implant allocation in a ratio of 2:1 (test:control), a total of 60 implants was needed to reach a statistical power of 90% ( $\alpha = 0.05$ ).

Randomization was realized by computer-generated random allocation, by means of numbered, sealed envelopes. Both investigator and patient were blinded until the actual implantation. Continuation of blinding was not feasible, because of observable differences in implant design. In our hospital, surgically placed implants are automatically recorded in the electronic patient file, which is also used for reporting during follow-up visits making postoperative blinding not feasible. Blinding of patients was also not feasible, because most patients were implanted under local anesthesia and could have overheard which type of implant was being installed.



**FIG. 1.** Skin height in relation to the abutment of the test implant (right) and control implant (left). *A*, Skin remains under the shoulder of the abutment; *B*, skin reaches between shoulder and rim of the abutment; *C*, skin is partially overgrowing the rim of the abutment; *D*, complete skin overgrowth of the abutment.

All implants and abutments were placed in a single-stage surgical procedure, using the, in our clinic at that time standardly applied, linear incision technique with subcutaneous soft tissue reduction (7). Surgery was performed between June 2012 and January 2014. Test and control implants were both loaded with the sound processor 3 weeks after surgery (range, 19–24 d).

Follow-up visits were scheduled at 7, 14, 21, and 28 days; 6 and 12 weeks; 6 months; and at 1, 2, and 3 years after implantation. During these visits, the ISQ was objectively measured by means of resonance frequency analysis (RFA), using a handheld Ostell® ISQ device (Ostell AB, Göteborg, Sweden), and a SmartPeg (type 55; Ostell AB, Göteborg, Sweden) attached to the abutment. Perpendicular measurements result in two values, where the lowest and highest values are recorded as an ISQ-low value and an ISQ-high value, respectively. Peri-abutment skin status was assessed according to the Holgers classification (16). The skin height was evaluated in relation to the abutment (Fig. 1).

### Data Analysis

Data management and statistical analysis were executed according to a predefined statistical analysis plan, and were performed by independent external data managers and biostatisticians (Statistiska Konsultgruppen, Göteborg, Sweden).

For comparisons between the test and control group, Mann–Whitney *U* tests were used for all continuous variables, Mantel–Haenszel  $\chi^2$  tests were used for all ordered categorical variables, Fisher's exact test was used for all dichotomous variables, and  $\chi^2$  tests were used for all non-ordered categorical variables. Repeated measures analyses were done for changes over time. The Wilcoxon signed rank tests were used for continuous variables, and sign tests were used for order categorical variables and dichotomous variables. Groups were compared according to the intention-to-treat principle. In case subjects were lost to follow-up, the last-observation-carried-forward method was used for ISQ measurements in the AUC calculations. Bilaterally implanted patients who received both a control and a test implant were included in both analyses for implant variables. Patients who received two tests or two control implants were represented by the mean of the two measurements for continuous variables or the worst value for categorical variables. For patient variables, bilaterally implanted patients who received both control and test implants were included in descriptive statistics but excluded in analyses on the patient level.

TABLE 1. Baseline characteristics

Variable	4.5 mm Implant Group (n = 39)	3.75 mm Implant Group (n = 20)	p
Gender			
Male	15 (38.5%)	9 (45.0%)	
Female	24 (61.5%)	11 (55.0%)	0.86
Age	53.7 (SD, 12.0; range, 23.0; 83.0)	53.0 (SD, 16.4; range, 19.0; 74.0)	0.50
Smoking	6 (15.4%)	6 (30.0%)	0.28
Acquired cond./mixed	26 (66.7%)	16 (80.0%)	0.37
Congenital conductive	1 (2.6%)	1 (5.0%)	1.00
Single sided deafness	13 (33.3%)	3 (15.0%)	0.27
Bilateral	3 (7.7%)	2 (10.0%)	1.00
Number of implants			
Single implant	36 (92.3%)	18 (90.0%)	
Two identical implants	1 (2.6%)	0 (0.0%)	
Two different implants	2 (5.1%)	2 (10.0%)	1.00

All tests were two-tailed and conducted at 0.05 significance level. All analyses were performed using SAS v9.4 (Cary, NC).

RESULTS

Patients

A total of 60 implants were consecutively placed in 57 patients. Three patients were implanted bilaterally in a single session; one of these patients received two test implants, and two patients received both a test and a control implant. Hence, in the analysis, the test group consisted of 39 implants and the control group consisted of 20 implants (14). All patients received their allocated treatment. No major perioperative complications were observed. Demographics and baseline characteristics are summarized in Table 1 and showed no statistically significant differences (14).

Two patients were withdrawn from the study. The first patient lost the implant spontaneously (control implant) after 31 months. The second patient had the implant (test implant) electively removed in another hospital after 24 months due to severe tinnitus, which

was thought to improve by performing a stapedotomy and afterwards fitting a normal air-conduction hearing aid.

Five follow-up visits, in five different patients, were missed or performed outside the defined visit window.

Implant Stability Quotient

The mean AUC for ISQ-low was 65.7 (SD, 3.4; range, 54.3–71.3) for the test implant (n = 39) and 61.4 (SD, 4.2; range, 51.4–67.6) for the control implants (n = 20). The inter-group difference of 4.32 ISQ-low points (range, 2.28–6.35; p = 0.0002) was statistically significant. The mean AUC for ISQ-high over the same period was 67.0 (SD, 3.3; range, 56.9–72.8) for the test implant (n = 39) and 63.7 (SD, 4.6; range, 52.5–70.8) for the control implants (n = 20). The inter-group difference of 3.29 ISQ-high points (range, 1.22–5.35; p = 0.006) was also statistically significant. Both results are displayed in Figure 2A and B. The mean increase in ISQ-low from baseline is statistically significant for both groups during all follow-up visits. For the test implant, however, both ISQ-low and high increased statistically significantly

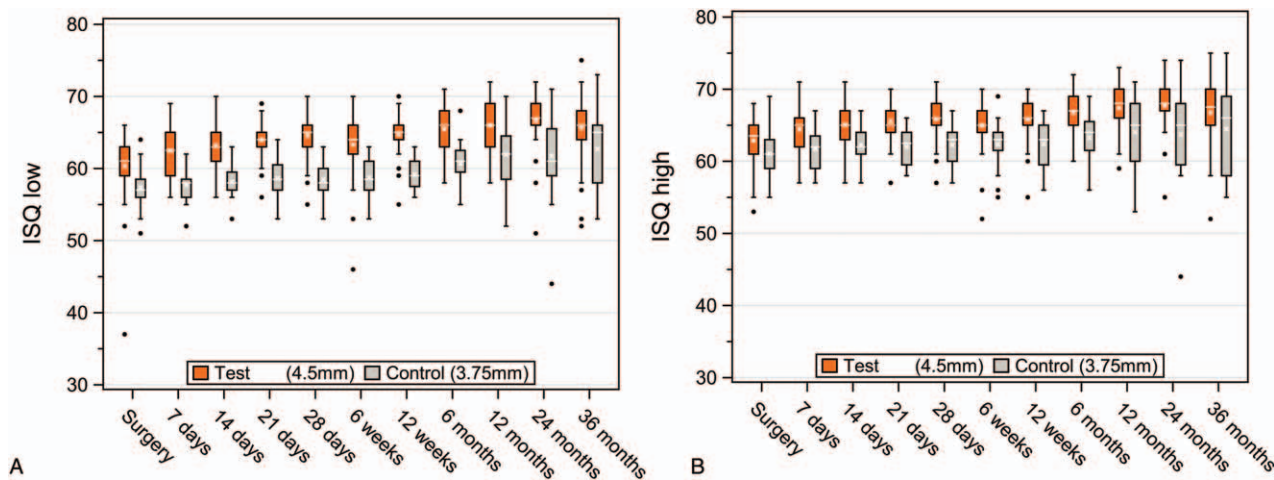


FIG. 2. A, Box-and-whisker plots of ISQ-low per implant; B, Box-and-whisker plots of ISQ-high values per implant. ISQ indicates implant stability quotient.

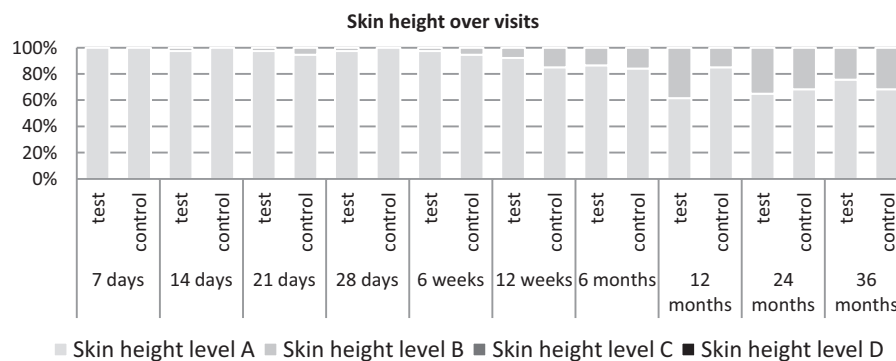


FIG. 3. Skin height per implant across visits.

more from baseline than for the control implant, but only during the first 6 months. During the 12 to 36 months visits, no ISQ-low and high inter-group differences in change between baseline were observed. When analyzing ISQ-trends, both implants showed increasing ISQ values up to 12 months, followed by period in which the ISQ remained stable until 2 years after surgery. Between the 2-year and 3-year visit, however, a statistically significant decrease was observed in the test group for both ISQ-high (0.72 ISQ-points,  $p = 0.013$ ) and low (0.78 ISQ-points,  $p = 0.032$ ). In the control group, no statistically significant decrease was observed in ISQ-low.

#### Implant Survival

No statistically significant difference in 3-year implant survival was observed (test 97.4% versus control 95.0%). One implant was electively removed in the test group, and one spontaneous implant failure was reported in the control group, 31 months after surgery. The loss occurred in a 21-year-old woman, a week after visiting our clinic because of progressive pain around the implant for months without signs of skin infection during any of her visits (Holgers 0).

#### Soft Tissue Tolerability and Complications

Three patients needed revision surgery of the soft tissue surrounding the implant; two in the test group

(5.1%) and one in the control group (5.0%). Two patients presented with thickened skin around the abutment resulting in persistent, unsolvable feedback issues 6 weeks, respectively, 9 months after surgery. The third patient (control), who suffered from psoriasis, presented with insufficient skin healing after 28 days.

Figure 3 presents an overview of soft tissue reactions per visit. Across all visits, Holgers grade 0 was observed in 84.5% (test) and 84.8% (control) of the visits; Holgers grade 1 in 14.0% (test) and 12.3% (control) of the visits; Holgers grade 2 in 1.5% (test) and 2.4% (control) of the visits; Holgers grade 3 in 0.0% (test) and 0.5% (control); and no Holgers grade 4 were observed during any of the visits. Adverse skin reactions (Holgers grade 2–4) were observed in 15.4% of the test implants and in 20% of the control implants. Neither these differences nor the analysis of other postoperative complications showed significant differences between implants: bleeding or hematoma in 2.6% (test) versus 4.9% (control); pain or numbness in 15.4% (test) versus 15.0% (control); and skin dehiscence in 7.7% (test) versus 10% (control).

Neither skin height during any of the follow-up visits, nor the maximum skin level across visits differed between groups (Fig. 4). However, in 55.9% of the implants (22 test implants and 11 control implants), skin height increased over time. No skin height levels C or D were observed. No difference in skin height was observed

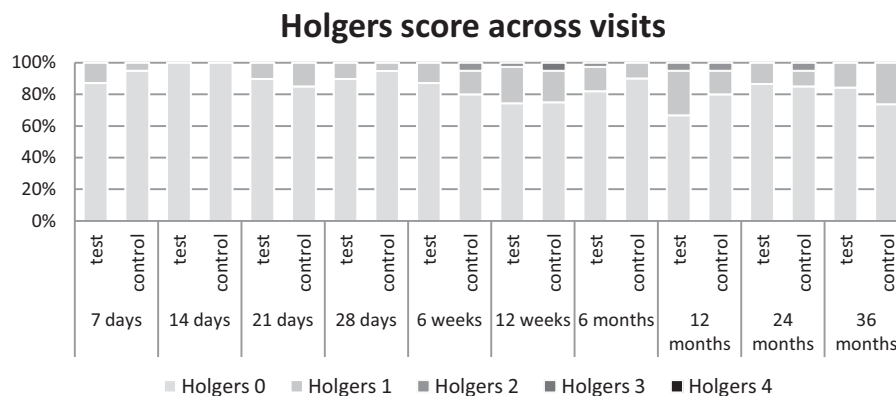


FIG. 4. Holgers score per implant across visits.

in patients who suffered from adverse skin reactions (Holgers grade 2–4) compared with those without adverse skin reactions.

## DISCUSSION

The current study, a continuation of a previously published 6-month report (11), is the first RCT comparing long-term outcomes of this specific wide diameter percutaneous bone-anchored hearing implant to the previous generation implant, both loaded with the sound processor at 3 weeks after surgery. These long-term outcomes encompassed implant stability and survival, ISQ-trend, and complications.

The current study has shown that during all visits, significantly higher ISQ-values were recorded for the test implant compared with the control implant. However, no differences in implant survival or soft tissue reactions were observed between implants. These outcomes confirm data from previous studies showing that wider diameter implants have significantly higher ISQ values, suggesting a higher implant stability. Therefore, earlier loading, i.e., after 3 weeks, could be advocated safe, as it does not influence survival rates of both implants (11,13).

Despite the extensive use of ISQ measurements in research, clinical and therapeutic consequences of absolute values are yet to be determined. For instance, a minimum ISQ-value to safely start loading the implant is lacking (17), although McLarnon et al. (18) adhered to a minimum of 60 ISQ points to safely load another wide-diameter implant, resulting in no spontaneous implant losses in the 4-month follow-up. However, ISQ itself is not a measurement of osseointegration, since multiple other factors—e.g., geometry of the implant and abutment, bone quality, and SmartPeg type—influence ISQ. This attributes to the difficulty of interpreting absolute ISQ values (17,19). Most of these factors were kept identical in both our study groups and remained unchanged during follow-up. Therefore, differences in mean absolute ISQ values for the groups as a whole could be attributed to the primary, or mechanical, stability, and osseointegration of the implant itself.

In the test group a minor decrease in ISQ was observed at the last follow-up, without clinically observed instability. Interestingly, a decreasing ISQ was also observed in two studies assessing a different wide-diameter implant. In the first study, the decrease occurred 2 years after surgery, but was overcome a year later (13). In the second study, a decrease occurred at the 3-year follow-up, but was also overcome at the 5-year visit (9,20). The dips were also minor and have not corresponded to clinically observed instability or implant loss. Thus, the clinical implication of the decrease in this study is to be determined by extending the follow-up of our patients.

With only one implant failure observed in each study group, the survival of both implants in this study was high at 97.4% (test) and 95.0% (control), respectively; moreover, only the implant failure reported in the control

group occurred spontaneously, a week after an extra visit for pain around the implant progressing for months. Interestingly, the mean ISQ of this specific patient gradually decreased from 59 (at surgery) to 44 (2 year follow-up), after which the implant was lost. Remarkably, this decreasing ISQ was observed without clinical signs of instability or skin infection. Nevertheless, no correlations between ISQ and implant loss could be made due to limited number of implant losses. Noticeably, during the physical examination at this subjects' last follow-up visit, manipulation of the abutment (tightening of or tapping on the abutment) resulted in significant increase of pain. These symptoms might suggest peri-implantitis, which is reported in dental implant literature (21). To our best knowledge, no report of peri-implantitis in bone-anchored hearing implants has been published. However, we did not assess whether loss of supporting marginal bone, defining peri-implantitis, was present in this patient. In addition, the biological mechanisms involved in late implant failures are obscure, particularly in the field of bone-anchored hearing implants. Future research is needed to unravel these mechanisms.

The implant loss rates of the test implant have previously been assessed by four prospective case studies with 1-year follow-up. Two studies used similar surgical techniques as in this study, while the two other studies used a tissue preservation technique. In none of the four studies, implant loss was observed (10,12,22,23). These are relatively short-term results; however, more than 50% of implant failures generally occur during the first year after surgery (2). These previous studies, therefore, cover this critical period.

The current study is the first RCT comparing the previous generation implant with the wide-diameter implant after 3 years of follow-up. Therefore, only studies assessing another wide-diameter implant with similar follow-up length can be used for comparison. This implant differs from our wide-diameter test implant by also having a moderately roughened surface and different abutment design. Two prospective studies reported equally high 3-year implant survival of 96.2 and 97% for these implants (9,13). It can be thus be concluded that the new generation wide-diameter implants show excellent implant survival.

The loading of both implants at 3 weeks after surgery seemed safe, as ISQ-trends increased and few implant losses were observed. Similar results with another wide-diameter implant have also been reported with loading times of 1 week (24), 2 weeks (25), and 3 weeks (12,13), confirming the safety of earlier loading with the sound processor.

Adverse skin reactions (Holgers  $\geq 2$ ) were observed sporadically and were equally distributed over both groups. This was expected since the implant diameter is not thought to significantly influence skin outcomes. It has previously been reported that the abutment shape, the angle between skin and abutment, and the used surgical technique, together with personal characteristics (as hygiene, skin type, skin disease, and age) do influence

these skin outcomes to a certain extent. The current set-up of the study is unique, since the only parameter changed is the diameter of the implant. The abutment itself is identical in both groups. All adverse skin reactions were successfully treated with a topical antibiotic/steroid ointment.

Other studies found similar low adverse skin reaction rates observed in patients with the same test implant. Foghsgaard and Caye-Thomasen (10) and Wazen et al. (12) observed adverse skin reactions in 2.6%, respectively, 0.6% of the visits with a follow-up of 1 year. Mowinckel et al. (22) and Hultcrantz (23) reported adverse skin reactions in 8%, respectively, 2.5% of the visits with a follow-up of 1 year. In addition, den Besten et al. (26) reported adverse skin reactions in 7.5% of the visits with a 6-month follow-up. However, in these three studies a different soft tissue handling technique was applied during surgery, i.e., soft tissue preservation instead of soft tissue reduction technique in current study (22,23,26). Two other studies using a different wide-diameter implant reported equally low adverse skin reaction rates of 1.8 and 0.9% after 3 years (9,13). It can be thus be concluded that the soft tissue tolerability of the new generation wide-diameter implants and abutments in combination with the applied surgical technique, personal characteristics, and after care is excellent.

As mentioned above, in many hospitals the tissue reduction technique has been replaced by the tissue preservation technique, due to shorter surgery time, cosmetic advantages, less numbness around the abutment, and similar or less skin complications (27). However, a single study also suggests a higher rate of adverse skin reactions for the tissue preservation technique in the first 6 months (26). Interestingly, when looking across the first 12 months follow-up in the same study, there was no longer any significant difference in adverse skin reactions between these techniques (unpublished data). Three year data will be available soon. This underlines the need for long-term comparative research to evaluate evolvments in surgical techniques.

To our best knowledge, this is the first study analyzing skin height after bone-anchored hearing implantation. Two patients underwent revision surgery for persisting, unsolvable feedback issues due to thickened skin touching the snap coupling, without partial overgrowth (skin height level B). Normally, we would have switched to a longer abutment. However, changing abutment length would have influenced ISQ data (our primary outcome) significantly. We therefore preferred skin revision. Both patients were informed and consented with revision surgery. Independent of the implant type used, skin thickened around the fixture in 55.9% of the patients. All patients have been operated using the linear incision with tissue reduction (7). Interestingly, skin thickening was only sporadically observed in the first 6 weeks (<4%), in 10% of the implants after 12 weeks, in 14% after 6 months, but it was observed around 27 to 34% of the implants after 12 to 36 months. No correlation with adverse skin reactions was observed. It could be possible

that thickening of the skin reflects the restoration of normal soft tissue after soft tissue reduction performed during surgery. It could also be the result of more active immunological mechanisms to compensate for the continuous breach in the mechanical defensive barrier of the skin implied by the skin-penetrating implant, regardless of surgical technique (28). In this light, the first 6-month evaluation of tissue preservation surgery versus tissue reduction surgery with this test implant reported no difference in skin height between groups (26). As previously discussed, however, most skin thickening in current study was observed after 6 months follow-up. Future, long-term research is, therefore, needed to investigate whether skin thickening differs between soft tissue reduction and tissue preservation surgery for bone-anchored hearing implantation. Nevertheless, the introduction of longer abutments in the past years will help to overcome possible problems with skin height (29).

The results of the current study are considered to reliably reflect clinical outcomes of both implants, due to the study design and data quality. The study design included a large population with adequate statistical power over a long-term follow-up period, only differing a single parameter between groups, i.e., implant design. Data quality is very high, with no patients lost-to-follow-up (except withdrawn patients) and five visits outside the predefined visit window. However, the non-blinded follow-up is a limitation, but a common trait of most implant studies. As discussed in the method section, continuation of blinding was not feasible, because of observable differences in implant design during surgery.

## CONCLUSION

In patients operated with the linear incision and soft tissue reduction technique, the 4.5-mm-wide test implant provides significantly a higher implant stability quotient (ISQ) compared with the previous generation 3.75-mm-wide implant after 3-year follow-up. Both test and control implant showed excellent survival rates. Adverse soft tissue reactions occurred sporadically, with no significant inter-group differences. Skin thickening occurred in the majority of the patients in both groups, but did not correlate with adverse soft tissue reactions. These long-term results of this prospective RCT indicate that the wide-diameter implant, for hearing rehabilitation in specific types of hearing loss, loaded with a sound processor at 3 weeks, is a safe and well-performing.

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