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Limitations of Titanium Dioxide and Aluminum Oxide as Ossicular Replacement Materials: An Evaluation of the Effects of Porosity on Ceramic Prostheses

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Background: Because the performance of titanium dioxide (TiO_2) has not yet been assessed in the unique environment of the middle ear, its role as an ossicular replacement prototype in the form of a total ossicular replacement prosthesis (TORP) was tested and compared with aluminum oxide (Al_2O_3), once considered to be a suitable implant material.

Methods: Ossiculoplasty was performed by implanting TORPs into the tympanic cavities of rabbits. After an implantation period of 28, 84, or 300 days, the petrous bones were extracted, whereby the biocompatibility of the prostheses was examined using light microscopy and scanning electron microscopy to determine morphologic changes in situ. Proper implant placement and functionality was tested via manual manipulation.

Results: Mucosa was seen covering most of the implants by day 84. Inflammatory cells were not observed in any of the specimens examined. The macroporous TiO_2 TORPs were subjected to osseous infiltration, material dissolution, and fragmentation, whereas the microporous TiO_2 implants were subjected to an increasing frequency of fissure formations. The Al_2O_3 prostheses demonstrated signs of material dissolution by producing encapsulated aggregates during the experimental trial period.

Conclusions: Neither the macroporous nor microporous oxide ceramics were able to withstand the oscillatory stress to which they were continually subjected. Although porosity allows for the rapid integration of an implant material into a biological environment, its properties are not suited to fulfill the requirements of strength and long-term stability, which are demanded of middle ear prostheses. **Key Words:** Aggregate—Fissure—Fragmentation—Imaging, three-dimensional—Perforations.

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The ossicular chain is assigned the job of adapting the differing impedances that naturally exist between a gaseous and liquid medium so that the transmission of acoustic energy in the form of sound waves between the two media is maximized. Pathologic processes within the tympanic cavity may, however, alter the normal transformer mechanism of the ossicular chain. Such processes or lesions interfere with the conduction of sound to the cochlea, causing a diminution of energy needed to stimulate the hair cells. Subsequently, conductive impairment generated by the damaged middle ear results in diminished hearing capability even though sensorineural hearing remains intact.

Chronic diseases involving the middle ear such as tympanosclerosis, cholesteatoma, and advanced otosclerosis result in conductive hearing impairment. Depending on the severity of the disorder, an increase in the hearing threshold can reach a range between approximately 40–60 dB (reviewed by 1,2). To quantify the extent of damage associated with conductive impairment, and thus the size of the air–bone gap, audiometry is frequently implemented.

Patients who have lost the ability to successfully conduct mechanical sound impulses can be treated with modern tympanoplasty (3–5). Types II and III have proven to be favorable solutions for patients suffering from conductive hearing impairment and/or loss (6). Choosing the appropriate material for the reconstruction or replacement of the ossicular chain has, however, proven to be rather controversial. Even though the healthy middle ear in humans is extremely tolerant towards the most obscure materials, the situation is reversed when examining an inflamed middle ear cavity. Most materials are then extruded or resorbed (7). In cases such as otosclerosis, chronic middle ear infection, and

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cholesteatoma, sanitized autogenic ossicles are not recommended for re-use since they contribute to the recurrence of the underlying disease (8,9). Autogenic or homogenic cortical bone is resorbed, whereas cartilage softens and weakens over time (8,10). Homografts pose similar risks because they are excellent carriers of infectious diseases such as hepatitis B and C, human immunodeficiency virus, and Jakob-Creutzfeldt's disease (8,11).

Alloplastic materials, on the other hand, seem to be a promising alternative to the aforementioned substances. Examples include: polymaleinate ionomer cement; synthetics (plastics such as polyethylene and polytetrafluorethylene); metals (stainless steel wiring, gold, platinum, titanium); and ceramics (vitreous ceramics, carbon, calcium-phosphate ceramics, ceramic oxides). Their biocompatibility and structural integrity make them suitable ossicular chain replacement material candidates that can readily adapt to the unique environment found within the tympanic cavity (12). According to Probst et al. (6), reconstructive ossicular chain tympanoplasty in the form of a partial or total ossicular replacement prosthesis (PORP or TORP) is presently the most common method for treating patients with significant conductive hearing impairment and/or loss. Therefore, the issue currently requiring attention involves the selection of an appropriate alloplastic material that can fulfill its duty as a permanent prosthetic implant. In essence, integration should be supported whereas immunologic rejection and biomechanically based extrusion should be avoided. Additionally, the implant material should be rigid and incorporated into its environment through bioactive bonding. None of the alloplastic materials currently available, however, fulfill all of these criteria.

Of the alloplastic materials, commercially pure titanium has successfully been used as an implant substance in the areas of traumatology, maxillofacial surgery, orthopedic surgery, and reconstructive cranial surgery (13–16). The metal and its alloys are readily formable and machinable. Titanium itself is known for its high degree of strength, minimal weight, corrosion resistance, and virtual nontoxicity (17,18). Recently, commercially pure titanium has also gained significant acceptance as an alloplastic material used in reconstructive ossicular chain tympanoplasty. Its successful performance was documented in experimental animal studies (19–21) and in clinical trials (22–27).

Oxide ceramics are also among the list of currently favored biocompatible substances on the market today. For instance, considerable preference has been given to titanium dioxide (TiO_2) because of its capability of demonstrating reduced implant surface ion release, especially in 0.1 M hydrochloric acid at 37°C (28,29). The hydrolyzed surface of the material adsorbs proteins (16,30), which allows for a direct interaction with cells and the extracellular matrix. Ceramics as a whole are also unique because their surface compositions can be varied by manipulating the manufacturing process (16). Thus, an implant material with a porous surface structure can be produced, which influences the interaction between the surrounding tissue and the implanted substance. In addition, porosity suppresses the development of fibrous capsules and inflammatory reactions, a key factor in promoting long-term stability and integrity (16).

In the past, another ceramic prototype, namely aluminum oxide (Al_2O_3), served as an ossicular replacement material. Its performance in the middle ear was well examined and proved to be successful in experimental animal studies (31,32). The prostheses were also tested in clinical studies involving the middle ears of patients suffering from conductive hearing impairment (4,33–35). Here, however, the implants often failed experimentally and clinically due to their lack of direct bonding to bone and relatively high extrusion rates (35–38).

This investigation analyzed the efficacy of the ceramic TiO_2 in its role as an ossicular replacement prosthesis prototype. For the purpose of this study, the differing porosities of the TiO_2 implant surfaces were tested. The authors could find no published data describing the biocompatibility and audiologic properties of TiO_2 in its role as an implant material in middle ear surgery. To compare the results collected for the TiO_2 prostheses, Al_2O_3 prostheses were also implanted in this experiment. The histologic reactions of the tympanic cavities and the structure of the TORPs in situ were evaluated during a 300-day trial period using a unique wet grinding technique, which allowed for a complete observation of the implants in their three-dimensional configurations.

MATERIALS AND METHODS

For this experimental animal study (no. 509c-42502-97/990, approved by the administrative district council of Hannover in accordance with paragraph 8 of the Animal Rights Act dated on May 25, 1998), a total of 29 approximately 6-month-old New Zealand White female rabbits originating from the animal breeding farm Charles River (Sulzfeld, Germany) were used in the examinations. The selection of the species was based on its similarity to human middle ear anatomy and the favored, standardized, microsurgical approach to the tympanic cavity (39–41).

The implants used for the surgical procedures were constructed of the ceramic materials TiO_2 (titania) and Al_2O_3 (alumina). Each prostbesis consisted of a round and flattened head (diameter, 2.7 mm; height, 0.5 mm) with a centrally placed and elongated hollow shaft (diameter, 0.6 mm; length, 3.7 mm). The individual weight of a single prosthesis averaged 0.10 g. The macroporous heads of TiO_2 implants exhibited a random distribntion of pores ranging between 10–50 μm in size. The microporous heads of the TiO_2 and Al_2O_3 implants exhibited pores ranging between 2–5 μm in size. The shafts of the prostheses were densely sintered and thus virtually without pores, regardless of the material used.

Before initialization of audiometric testing and implantation, the rabbits were sedated with an intramuscular injection of 25 mg/kg of ketamine (Ketanest, Albrecbt, Aulendorf/Württemberg, Germany) and 5 mg of dormifacient (Midazolam, Cura-Med, Hameln, Germany). Anesthesia was induced with 1 mg/kg of 1% Propofol-Lipuro (Braun, Melsungen, Germany)

intravenously, followed by 5 mg of the anticholinergic agent Robinul (Riemser, Insel Riems, Germany) intramuscularly and 5 mg of the analgesic Temgesic (Essex Pharma, München, Germany) subcutaneously. After endotracheal intubation, narcosis was maintained with 1.5% isoflurane (Forene, Abbot, Wiesbaden, Germany). An infusion of 10 ml/kg/h of Sterofundin–HEG-5 (Braun) was used to stabilize the animals' circulatory systems.

Directly before the implantation of the TORPs, as well as at 28, 84, and 300 days after implantation, electric response audiometry was used to determine the hearing thresholds of the animals. The generated results were measured in dB normalized hearing level using the click stimulus, which involved an alternating polarity for a duration of 100 μs at frequencies between 0.5 and 6 kHz and in dB peak equivalent sound pressure level using the pip stimulus involving a frequency of 8 kHz. (42)

The TORPs were implanted in the right middle ear cavity with the help of an OPMI Twin ER (Zeiss, Ober-Koehan, Germany) laser microscope. The left middle ear of each animal remained unscathed and served as a control. After creating a retroauricular opening, along with a tympanomeatal flap, the transection of the incudostapedial joint was performed using an erbium–yttrium-aluminum-garnet laser with a toral of 20 impulses at 30 mJ. The incus was separated from the head of the malleus using 30 impulses at 50 mJ. In a final step, the stapes superstructure was separated from the crura of the stapes using 20 impulses at 15 mJ. Residual organic debris resulting from intraoperative manipulation was not allowed to remain within the tympanic cavity. An unhindered placement of the implant between the tympanic membrane, the remaining manubrium of the malleus, and the stapes footplate was performed by individually adapting the size of each prosthesis. In 5 of the 29 animals, the additional removal of osseous spurs overlying the facial nerve canal was required so as to avoid conflicting contact between these structures and the implanted TORPs. To avoid excessive formation of granulation tissue at the cartilage/bone interface of the auricular canal, silicone-based foils and tamponades (Gilitta; Braun) soaked in doxycyclin (Ratiopharm, Ulm, Germany) were deposited at this site. The wound rims were adapted with Vicryl suture material (4/0 1.5 metric, SH-1 plus; Ethicon, Norderstedt, Germany) and closed with Mersilene (2/0 3.0 metric; Ethicon) button sutures. After surgery, 10 mg of antibiotics Baytril (Bayer Vital, Leverkusen, Germany) were given per OS for 10 days.

The randomly distributed animals had the macroporous TiO_2 prostheses implanted for 28 days (n = 3), 84 days (n = 4), and 300 days (n = 4). The designated trial period for the microporous TiO_2 prostheses was identical: 28 days (n = 4), 84 days (n = 4), and 300 days (n = 5). The disadvantages of the Al_2O_3 prostheses recognized during the experimental trials limited the number of animals to n = 1 for 28 days, n = 2 for 84 days, and n = 2 for 300 days.

For histologic analysis, both middle ear cavities were perfused with 4% glutaraldehyde (w/v; Merck-Schuchardt, Hohenbrunn, Germany) in 0.1 M phosphate-buffered saline (PBS; pH 7.4) (Gibco PBS Tablets; Gibco, Paisley, U.K.) at room temperature. The petrous bones were then dissected and the bulla tympanica was opened at a 45 degree angle to the plane of the tympanic cavity. The position of the prosthesis within the tympanic cavity was documented using a camera (OM4-Ti Camera; Olympus Optical [Europe], Hamburg, Germany), which was attached to an operative microscope (OPMI Twin ER). Artificial debris resulting from postoperative tympanic cavity preparation was not found within the specimens on macroscopic and microscopic examination. In addition, a functionality test of each prosthesis was performed using a pair of forceps.

After further fixation for 24 hours at 4°C with 4% glutaraldehyde (w/v) in PBS, the specimens were dehydrated with increasing concentrations of acetone (J.T. Baker B.V., Deventer, The Netherlands) and then dried using the critical point method (CPD 030; Balzers, Liechtenstein). After evacuation (Duran Exsiccator; Schott Glas, Mainz, Germany), the dried specimens were embedded in epoxy resin (Hysol Resin Epoxy + Hysol Hardener; Dexter, Olean, NY, U.S.A.). The addition of EPO Blue Contrast Coloring (Wirtz-Buehler, Düsseldorf, Germany) allowed for a better contrast of the embedded specimens.

Sectioning of the individual planes of the tympanic cavity was performed by wet sanding with silicon carbide grinding paper (SiC Paper; Struers A/S, Rodovre, Denmark) in a sanding and polishing machine (LaboPol-5; Struers A/S). The polished surfaces of the specimens were stained with hemalum (Mayer's Hemalum Solution; Merck, Darmstadt, Germany) and 1% eosin y (w/v) (Certistain Eosin Y; Merck) diluted in 70% ethanol. The various planes were documented with a stereoscopic microscope (MZ-6; Leica, Bensheim, Germany) and a light microscope (Orthoplan; Leitz-Wetzlar, Werzlar, Germany) using an external liquid crystal display light source (KL 1500; Leica, Bensheim, Germany), which projected light downward onto the specimen blocks. The images produced by a 12-bit charge-coupled device digital camera (Color View 12; Soft Imaging Systems, Lakewood, CO, U.S.A.), which was attached to the light microscope, were analyzed with Analysis 3.1 (Soft Imaging Systems) and processed with Adobe Photoshop 5.0 (Adobe Systems Inc., San Jose, CA, U.S.A.).

For the examinations involving scanning electron microscopy, the prostheses were extracted from the tympanic cavities and fixed with 2.5% glutaraldehyde (w/v) and 2% paraformaldehyde (w/v) (Fluka, Buchs, Switzerland) in 0.1 M sodium cacodylate, pH 7.3 (Merck-Schuchardt) for 6 to 8 hours at 4°C. The implants were then postfixed with 2% osmium tetroxide (w/v) (Polysciences, Warrington, PA, U.S.A.) in the same buffer for 90 minutes at room temperature. After dehydration with increasing concentrations of acetone, the prostheses were desiccated using the critical point drying method. Both the implanted and nonimplanted prostheses were mounted on aluminum thumbtack holders using conductive taping (Plano, Wetzlar, Germany) and coated with a 30-nm thick layer of palladium/gold alloy in the Polaron E 5400 High Resolution Sputter Coater (Polaron Equipment Ltd., Watford, U.K.). The digital photomicrographs generated by the Philips Scanning Electron Microscope 505 (Philips, Eindhoven, The Netherlands) were processed using SEM 3.0 Digitizing Software for Electron Microscopes (A. Gebert, University of Lübeck, Lübeck, Germany; and G. Preiss, Department of Cell Biology–Center for Anatomy, University Hospital Hannover, Hannover, Germany).

RESULTS

Scanning electron microscopy revealed that the macroporous TiO_2 prostheses' heads were covered with a nonuniform distribution of large pores, whereas the shafts displayed a smooth surface (Fig. 1A and C). The heads of the microporous TiO_2 (Fig. 1B) and Al_2O_3 prostheses were uniformly manufactured. The transition zone between the densely sintered shaft and the microporous head could clearly be seen (Fig. 1D). After implantation,

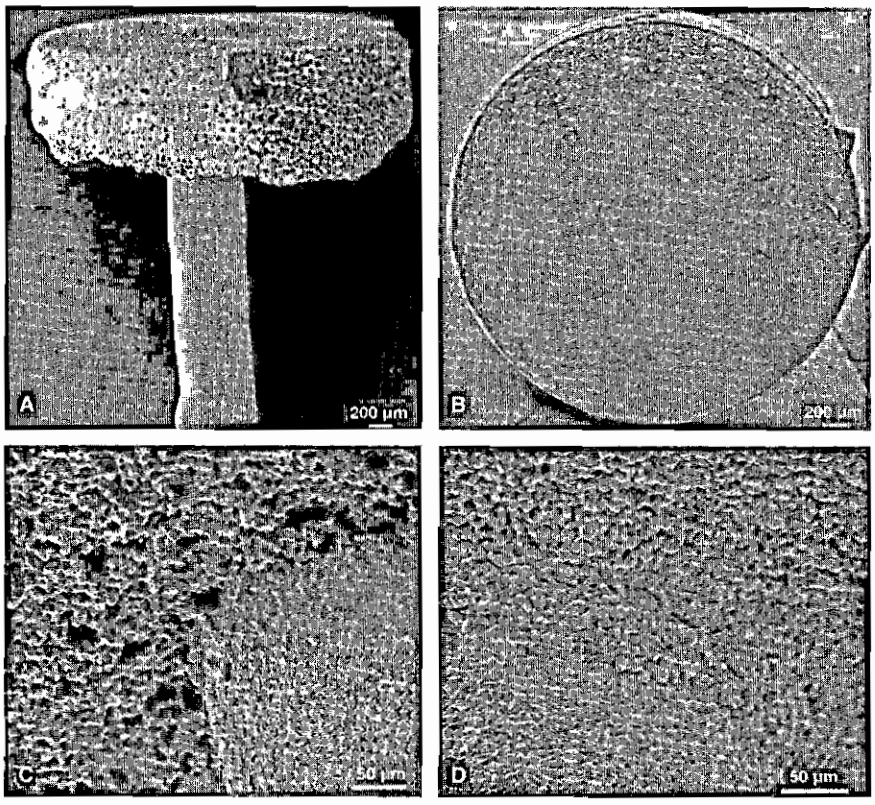

FIG. 1. Scanning electron micrographs revealing the macroporous TiO_2 (*A, C*) and microporous TiO_2 (*B, D*) ceramic prostheses before implantation. The junction between the head and shaft of a macroporous (*C*) and microporous (*D*) TiO_2 TORP is shown in comparison.

both the TiO_2 and Al_2O_3 TORPs were well tolerated during the duration of the experimental trial period (Fig. 2A–C). The mucosa of the tympanic cavities generally remained free from irritation and inflammation. Anatomic anomalies resulting from surgical intervention were not observed. Tympanic membrane reaction as related to implant presence remained neutral. The external auditory meatuses were found to be nonirritated and free from hindering debris. By day 84, however, tympanic membrane thickening and protrusion was evident in both of the specimens containing the Al_2O_3 prostheses. Implant extrusion did not occur in any of the specimens during the 300-day implantation period.

Mucosa

After 28 days of implantation, all of the prostheses displayed partial epithelial coverage. In most cases, the heads and shafts of the prostheses were draped with a fine mucosal tunic (Fig. 2A and B). By day 84, mucosal coverage of the macroporous TiO_2 prostheses and Al_2O_3 prostheses was complete, whereas the microporous TiO_2 implants were nearly fully enveloped (Fig. 2C and E). The morphology of the epithelial surface was comparable to that of the adjacent mucosa lining the tympanic cavity. This was confirmed using scanning electron microscopy (Fig. 3). After 300 days, an increase in epithelial thickness was only seen in the specimens containing the Al_2O_3 implants (Fig. 2F). Further changes in the mucosal morphology of the TiO_2 TORPs were not evident (Fig. 2D).

Scar tissue

In general, delicate strands of connective tissue underlying the mucosa were seen surrounding the shafts of the microporous and macroporous TiO_2 prostheses by day 28 (Fig. 2A and B). Localized areas of thickening were detected at the junction between the head and shaft, which remained unchanged during the implantation period (Fig. 2). Thicker, more fibrous strands of connective tissue were, however, seen encasing the heads of the macroporous TiO_2 implants (Fig. 2A). In some of the specimens containing the macroporous prostheses, strands of scar tissue could be seen fastening the TORPs to the lateral and medial walls of the tympanic cavity. Vascularization of the surrounding tissue was delicate and only sporadically represented in the macroporous and microporous TiO_2 prostheses.

In comparison, dense connective tissue formation could be seen surrounding the Al_2O_3 prostheses, especially concentrated in the area of the head/shaft interface (Fig. 2C and F). Fibers were seen connecting the implants to the boundaries of the tympanic cavity (Fig. 2C). During the course of the implantation period, scarring increased slightly. Large blood vessels penetrated the collagen fibers in the vicinity of the implants. The mucosal surface surrounding the Al_2O_3 shafts had a granulated appearance.

Ectopic ossification

Newly formed bone tissue was evident in all of the specimens and was found to be in direct contact with the

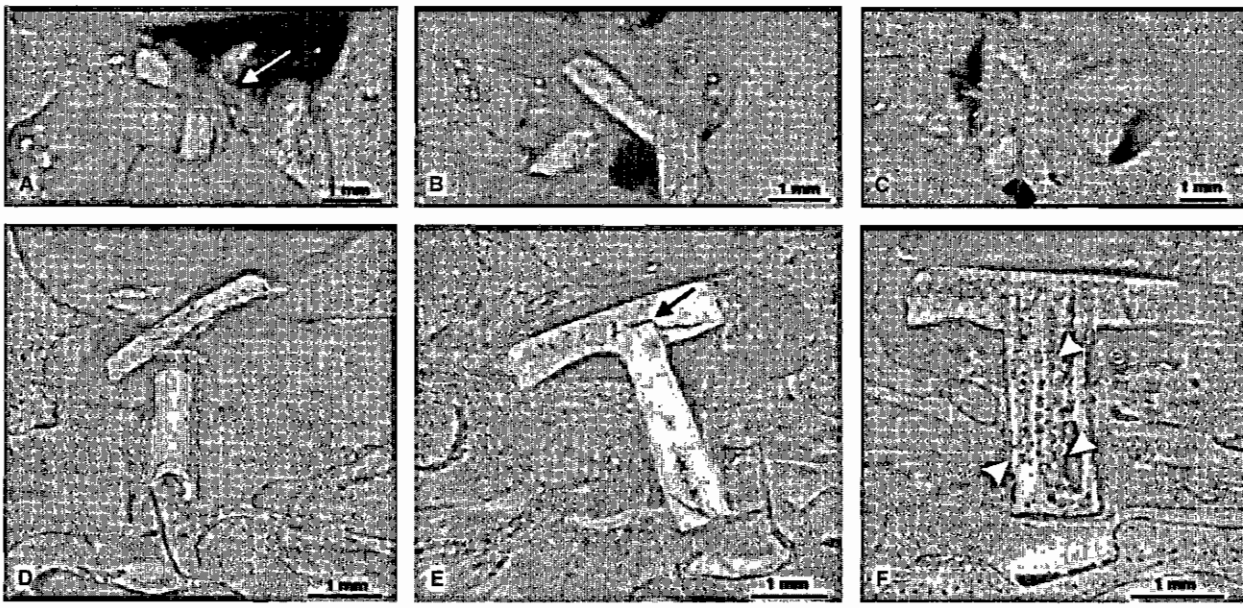

FIG. 2. Macroscopic photographs (*A–C*) depicting the in situ orientation of a macroporous TiO_2 (*A*), microporous TiO_2 (*B*), and Al_2 (*C*) TORP. Scar tissue can be seen covering the macroporous TiO_2 prosthesis head and a portion of the proximal shaft (*arrow in* Delicate collagen fibers are seen fixating the microporous TiO_2 implant at the junction between the head and shaft. Dense connect tissue is observed encasing the entire Al_2O_3 implant (*C*). The corresponding histologic micrographs of the wet ground specimen plan stained with hemalum and eosin y (*D–F*) reveal the fate of the TORPs on being subjected to a longer implantation period. A compl separation at the head/shaft interface is visible in the macroporous implant (*D*), whereas fragmentation (*arrow*) is evident in microporous TiO_2 TORP (*E*). The shaft of the Al_2O_3 prosthesis contains several material defects (*arrowheads in F*).

implants without the interposition of any other type of connective tissue (Fig. 4A, E, and F). The macroporous TiO_2 TORPs initiated the strongest osseogenic response. Ectopic bone formation on these prostheses was evident on the outer surfaces of the shafts by day 28, and expanded to include the inner shaft surfaces as well as the upper and lower planes of the heads by day 84. Complete osseous infiltration of the pores was evident after a longer implantation period (Fig. 4A and G).

The microporous TiO_2 implants were subjected to delicate ectopic ossification on the outer surface of the shafts after 28 days of implantation. The heads and the inner surfaces of the shafts demonstrated sources of new bone formation by day 84. These areas of newly formed bone tissue only modestly expanded between day 84 and 300 (Fig. 4E and H). Bone tissue was not significantly concentrated in regions where the TORPs were exposed to fragmentation (Fig. 4B).

Newly formed bone tissue was not visible in the specimens containing the Al_2O_3 prostheses after 28 days of implantation. By day 84, discrete areas of ectopic ossification could be seen lining the surfaces of the heads. After an implantation period of 300 days, new bone formations were observed expanding along the inner and outer shaft surfaces. The regions of the shafts displaying material defects were filled with both connective and bone tissue (Fig. 4I).

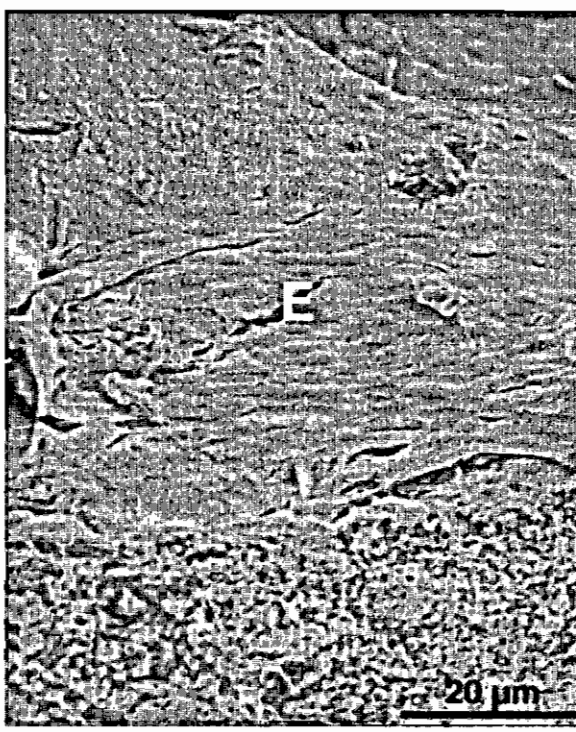

FIG. 3. Scanning electron microscopy revealing polygo squamous epithelium (E) covering the shaft of an Al_2O_3 TO after 84 days of implantation.

Material stability, rigidity, and surface properties

Individual intraoperative adjustability and fitting was performed by selectively sizing the TiO_2 and Al_2O_3 im-

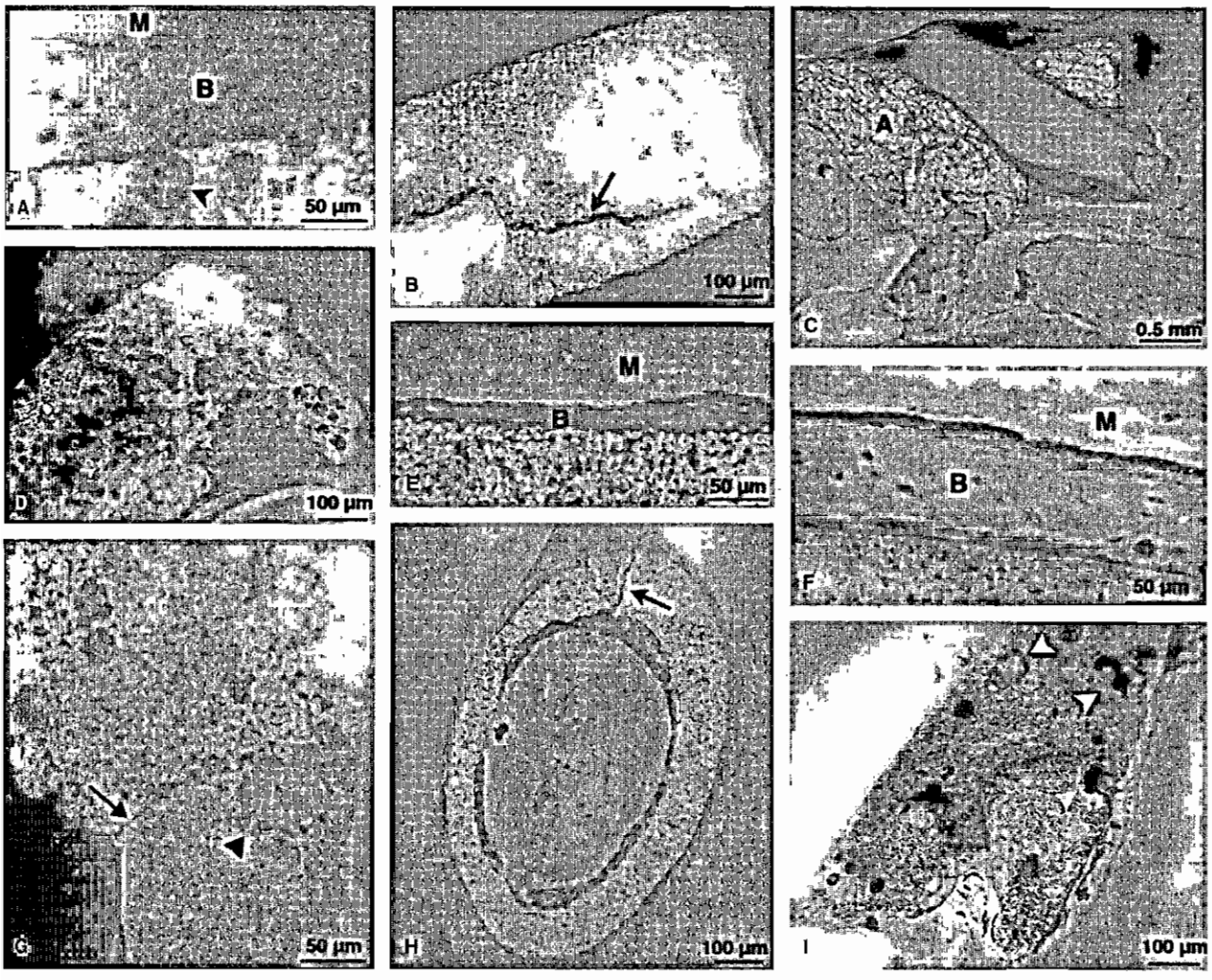

FIG. 4. Histological specimen planes showing the macroporous TiO_2 (*A, D, G*), microporous TiO_2 (*B, E, H*), and Al_2O_3 (*C, F, I*) prostheses after staining with hemalum and eosin y. Osseous infiltration (*arrowheads in A and G*), material dissolution (*D*) and fissure formation (*arrow in G*) is observed in the macroporous TiO_2 prostheses after 84 days of implantation (M, mucosa; B, bone). The microporous TiO_2 TORPs reveal fissures (*arrow in H*) and fragmentations (*arrow in B*) after longer implantation periods. Ectopic ossification is seen on the surface of the implant material (*E, H*). By day 84, the Al_2O_3 prosthesis is surrounded by aggregates (A), whereby several areas of dissolution in the shaft are visible (*C, arrowheads in I*). Beneath the mucosa, newly formed bone tissue exists in direct contact with the TORPs (*F*).

plants with a scalpel. Material integrity and stability was not compromised by the sizing process. Signs of erosion, abrasion, and fissure formation were not observed. This was confirmed by scanning electron microscopy (Fig. 1).

During the experimental trial period, the macroporous and microporous TiO_2 prostheses developed isolated fissures. By day 84, there was an increasing tendency toward fracturing in both TiO_2 implant types, especially at the head/shaft interface (Fig. 4B and G). After 300 days of implantation, the fractures increased in magnitude, whereas the fissures expanded to include the prostheses' shafts (Fig. 4H). The numerous fissures detected in both the heads and shafts resulted in a multifragmented representation of the TORPs (Fig. 4B, G, and H).

The macroporous TiO_2 prostheses were additionally plagued by abrasions and erosions. These defects were especially visible on the upper and lower surfaces of the prostheses' heads and tended to increase in magnitude during the implantation period (Fig. 4A, D, and G). Therefore, it could be ruled out that the newly observed pores were preformed during the manufacturing process. Connective tissue and bone were seen penetrating the porous structure of the ceramic. The escalating instability of the macroporous substance was responsible for the separation of the head from the shaft in most of the specimens by the end of the elapsed trial time (Fig. 2D).

Peculiar encapsulated aggregates were detected in the connective tissue surrounding the shafts of the Al_2O_3 TORPs after an implantation period of 28 days. By day 84, the size of the aggregates had increased, whereas material defects in several areas of the shafts were seen in parallel (Figs. 2F and 4C and I). Because the virtually

pore-free construction technique implemented by the manufacturer was the same for all three of the implanted prostheses types, this observation proved to be unique. As a result of the fact that the increase in aggregate dimension was directly correlated with the size of the defects in the Al_2O_3 shafts, it was hypothesized that the disintegration of the prostheses commenced within the tympanic cavity. At first, the defects were filled with connective tissue; shortly thereafter, bone developed within the cavities (Fig. 4I). Giant cells around the encapsulated aggregates were not detected. The capsules consisted predominantly of fibrous connective tissue.

Fissure formations in the heads and head/shaft interfaces of the Al_2O_3 prostheses were not detected during the trial period. Because Al_2O_3 had a strong affinity for the hemalum solutiou, existing defects may have been camouflaged by the staining process. Thus, it could not be determined whether fissures and fragmentations were absent or simply masked by the intense staining of the Al_2O_3 implant material.

Biomechanics and functionality of the implants

The oscillatory capability of the macroporous TiO_2 prostheses, as demonstrated by the manually navigated functionality test in situ, tended to decline during the trial period. Because of the increase in fibrous connective tissue observed between days 28 and 300, the TORPs were ultimately subjected to an increasingly restricted motility. Some specimens also demonstrated partial displacement of implant positioning due to the directional pull of the connective tissue. In contrast, the microporous TiO_2 prostheses were flexibly encased by the surrounding connective tissue and appropriately oriented between the tympanic membraue and the remaining stapes crura. Consequently, sufficient oscillatory motion of the prostheses was noted during each of the trial periods. The Al_2O_3 prostheses, which were surrounded by encapsulated metallic aggregates, tended to be displaced from their original implant position within the tympanic cavity. Nevertheless, stimulation of the malleus manubrium via forceps continued to be successful in setting the rudimentary crura of the stapes into motion.

DISCUSSION

In several experimental animal studies involving ossicular replacement materials, the compatibility of commercially pure titanium was evaluated by analyzing a limited number of specimen slides at the transition zone between the implant surface and the surrounding tissue (19–21). The implants were generally coated with mucosa. Neither inflammatory intolerance nor extrusions of the prostheses were noted. Although the mucosal and submucosal layers covering the implants were thicker and provided evidence of granulation tissue in comparison with normal tympanic mucosal tissue by day 28, changes in reactive tissue development were evident by day 84. At this point, the increased breadth of the submucosal layers had reverted to their original width and appearance. This adaptation process continually progressed up to day 168. In addition, the prostheses were generally noted to be encased by strong connective tissue fibers running parallel to the implants between the tympanic membrane and the oval niche near the remaining footplate (20,21). As documented in this investigation, integration of both the macroporous and microporous TiO_2 prostheses occurred without complications. These observations were verified by the systematic analysis of the implant layers in situ. Direct physical contact was established between the surface of the implants and the overlying tissue. The prostheses were firmly bound to the rudimentary crura of the stapes by newly formed bone and connective tissue.

In clinical trials, titanium prostheses were shown to be well tolerated by patients suffering from chronic middle ear disease (24,25,27). Cellular inflammatory responses at the implant surface were not observed in tympanic cavities displaying inflamed and granulated mucosa. Scar tissue development was only seen in middle ears, which had undergone repeated invasive surgery as a result of the underlying disease (implanted 2–15 mo) (24). In addition, prosthesis extrusion was not observed in cases involving ventilatory dysfunction of the auditory tube with subsequent tympanic membrane retraction (27).

In experimental animal studies involving rabbits, Al_2O_3 prostheses were noted to be completely covered with delicate mucosa within a brief time interval (31,32). Additionally, it was shown that porous, hollow bodied Al_2O_3 cell carriers, which were implanted into the abdominal walls of rats, displayed no signs of fibrous encapsulation (16). Neither inflammatory cell reaction nor irritation of the muscle cell wall during implant integration could be seen. However, after an implantation period exceeding 4.5 months, researchers were able to document the development of increased fibrous tissue density surrounding implanted Al_2O_3 prostheses in the tympanic cavities of rabbits (31,43). As a result of the complete analysis of the various planes representing the wet ground Al_2O_3 prostheses, the present investigation demonstrated that the densely packed fibrous connective tissue contained aggregates of the dissolving implant.

In the past, the presence of multinucleated foreign body giant cells within the tympanic cavity and how they interact with various implant materials has been a subject of impassioned debate. Numerous authors disagree on both the significance and fuuction of these cells in association with alloplastic materials. The investigations undertaken in this study confirmed the absence of multinucleated giant cells in all of the specimens. Although other experimental animal studies involving rabbits detected the existence of foreign body giant cells on the surface of Al_2O_3 prostheses as early as 3 weeks after implantation (31), clinical trials often reported of differiug results. Foreign body reaction was not seen in patients who had received Al_2O_3 implants (44). Yamamoto and Iwanaga (38) reported on the presence of foreign body reaction and extrusion occurring only in middle ears displaying

unfavorable conditions (acute infection, chronic disease, etc.).

Nevertheless, the presence of interstitial aggregates surrounding the Al_2O_3 implants in this study initiated a cause for concern. The dimensions of these aggregates were directly correlated with the continually increasing size of the shaft perforations. Because the investigations undertaken by Woodman et al. (45) were able to verify that the concentration of aluminum, which had been implanted as prosthetic bone replacement material in monkeys, increased linearly in the animals' adjacent muscle and lymph tissues over a period of 8 years, its use as an implant material has been viewed critically. Traces of the metal were also found to be accumulating in the lungs, kidneys, and hearts of these animals. The clinical significance of these results calls for a certain degree of caution and awareness when considering the long-term implantation of various metals with respect to their toxic and carcinogenic effects.

Material surface properties

According to Wintermantel et al. (16), the biocompatibility of alloplastic materials is divided into two categories: surface and structural compatibility. Surface compatibility is defined as the physical and chemical interaction between the outer molecular layers of the alloplastic material and the directly adjacent cellular layers. Structural compatibility is primarily defined as the ability to transfer forces. To achieve long-term compatibility and stability, an implant material must incorporate both components to a sufficient degree.

Regarding the first category of biocompatibility, proper material surface topography plays a key role in the initiation of biointegration. Integral proteins found in the plasma membranes of cells allow for the attachment of the cells to the adsorbed proteins located on the surface of implant materials (16). Thus, a biomaterial that provides a large surface area favors tissue integration. The in vitro behavior of surface protein adsorption as it relates to commercially pure titanium and Al_2O_3 was studied by Schwager (25). In essence, it was concluded that protein desorption rates were greater for Al_2O_3 than they were for titanium. The results of this study show that the amount of newly formed bone in the specimens containing the Al_2O_3 TORPs was less than the amount found in the specimens containing the macroporous and microporous TiO_2 TORPs. This may have been related to the higher desorption rates associated with Al_2O_3. The greater rate of ectopic ossification seen in the specimens containing the TiO_2 implants supports the theory of improved osseointegration that is associated with titanium.

In addition to adequate protein adsorption, the selection of an appropriate ceramic pore size is of fundamental importance when planning for optimal material surface topography. As shown in the current study, the surface structure of a ceramic material can be manufactured in such a manner that either a dense or porous form exists as a final product. The two forms, although similar in chemical composition, have differing effects on the mechanical and biological properties of the prosthesis as a whole (16). As indicated by the results, the macroporous TiO_2 TORPs were subjected to an increasing amount of material dissolution during the elapsed trial time. In the past, the differences between the amplified and reduced porosities of TiO_2 ceramics were tested in vitro (46). Compositions with a high degree of porosity, and thus permeability, were subjected to wear particle release on being exposed to osteogenic cell lines. Compositions with reduced porosities were of a markedly higher strength. Noticeable signs of dissolution were absent. It was concluded that a ceramic material demonstrating surface porosity should be optimized to a level at which the release of wear particles is not observed on exposure to tissue culture.

In the experimental animal studies undertaken by Grote et al. (47) both macroporous (100 μm) and microporous (3 μm) hydroxyapatite middle ear implants were tested over the course of 1 year. Initially, the macroporous implants were filled with exudate and fibrous tissue. During the trial period, the quantity of fibrous tissue increased, whereas bone tissue development was observed in the pores. Morphometric analysis confirmed a direct correlation between pore size and the amount of migratory tissue ingrowth. Macroporous expansion increased by 69% over the course of 1 year. In contrast, pore expansion was not observed in the dense (3-μm) implants. Neither resorption nor extrusions of comparably dense hydroxyapatite middle ear prostheses were noted during clinical trials (48,49).

As evidenced, the smaller the pore sizes, the greater the overall compatibility of the implanted prosthesis. In essence, dissolution is less likely to occur. This is comparable to the solid, nonceramic middle ear prostheses currently in use. In in vivo experiments, polymaleinate ionomeric prostheses were not subjected to dissolution or degradation, even after 2 years of implantation time (21,50–52). It was proposed that the density of the implants prevented the ingrowth of cellular components; consequently, material debris was absent (52). The same was found to be true for commercially pure titanium (19–21,24,25).

Additional consequences of porosity become apparent when examining the functional results provided by audiometry. Those animals that received the macroporous TiO_2 prostheses demonstrated a continually higher level of conductive hearing loss than did those animals that received the microporous (TiO_2 or Al_2O_3) implants. As a result of the similar structural properties of the microporous implant types, a more optimal interaction between the surrounding tissue and the implant surface was established (42).

Webster et al. (53) recently proposed a new theory involving the microscopic surface topography of ceramic materials. Their study provides in vitro evidence of the ability of nanophase TiO_2 and Al_2O_3 to simulate the material characteristics of physiological bone (surface grain size), which enhances subsequent osteoblast adhesion. In the presence of 10% fetal bovine serum, osteo-

blast adhesion on the nanophase-based TiO_2 and Al_2O_3 ceramics (32-nm and 23-nm grain sizes, respectively) was significantly greater than on conventional TiO_2 and Al_2O_3 (2.12-μm and 177-nm grain sizes, respectively). In essence, an increase in surface aqueous wettability, hydrophilicity, and overall surface area of the nanophase material was noted. The authors imply that there is a possible "critical grain size (between 49 and 67 nm for Al_2O_3 and between 32 and 56 nm for TiO_2) that plays a crucial role in mediating osteoblast adhesion to nanophase ceramics" (53). The study concludes by stating that specific material chemistry is not the deciding factor regarding cellular attachment to the surface of implant materials, but rather the optimal surface topography in the nanometer range. Similar supporting evidence as it relates to cellular adhesion was shown by Elbel et al. (54). The in vitro experiments demonstrated that cardiomyocytes maintained their original rod-like cell morphology on attachment to nanophase TiO_2. The overall rate of cellular attachment was greatest with this material.

Although density has its advantages, the benefit of porosity should not be disregarded. Porosity regulates the rate of ectopic bone formation and thus influences the effect that osseointegration has on implant materials. Therefore, the conclusions drawn from the two aforementioned studies are of utmost relevance with regard to the positive and negative aspects of osseointegration, especially when involving ossicular replacement prostheses. On the one hand, the increased surface reactivity of nanophase ceramics allows for rapid integration in the sense of a seamless transition between the implant material surface and the surrounding bony structures (vestigial stapes crura or footplate and remaining malleus manubrium if present). This ensures the establishment of a secure bond between the implanted prosthesis and the remaining ossicular components, which is needed for adequate sound conduction. On the other hand, the miniscule microporous structure allows for overall greater strength and resists the disadvantages associated with osseous infiltration.

Material strength, stability and rigidity

Structural compatibility of an alloplastic substance is based on its strength and inertness. These properties are required to ensure the long-term stability of an implant material. Thus, the second category of biocompatibility as it relates to alloplastic materials is represented. The inert behavior of an alloplastic material is also important when considering the adverse response or immunologic rejection that could be initiated by the surrounding cells (12). Therefore, inert metals such as gold, steel, and titanium have long been used as prosthetic implants to assure long-term solidity and to ward off the tribulations associated with degradation or dissolution.

Recently, however, researchers claimed that a release of titanium ions occurs at low pH levels. It was hypothesized that the naturally occurring outer oxidized layer of commercially pure titanium is uot strong enough to prevent the release of ions from the material's surface (29 Consequently, it was speculated that the stability of pu titanium could be increased upon further oxidation (28 This theory was tested by recording the ion release fro commercially pure titanium and TiO_2 during a 12-wee period of submersion in various solutions. The release titanium ions from TiO_2 was absent in all of the teste solutions, whereas ion release from commercially pu titanium was evident in both 0.02 M lactic acid and 0 M hydrochloric acid (28,29). Based on these observ tions, it was assumed that oxide ceramics would provi for the surface and structural compatibility required of prosthesis on being subjected to the unique environme of the middle ear.

However, the numerous fissure formations and fra mentations displayed by the microporous TiO_2 implan demonstrated that this material was brittle and could n withstand the continuing oscillatory stress to which was permanently subjected. Therefore, it becomes ne essary to evaluate the cause of these disturbances. Upo selecting titanium (99.75% purity) as a substrate used ceramic sintering, it is imperative that the iron content the metal be known. By increasing the iron content fro 0.05% to 0.5%, the strength of titanium can be double (55). The long-term risks associated with corrosion a increased, however. If, on the other hand, the iron co tent of titanium were reduced to 0.005%, the met would become so soft that it would be difficult to pro erly mold. Perhaps one of the answers to the controve sial outcome representative of the current study can l explained by this phenomenon. In addition, a furth clarification of the results might be explained on reviev ing the manufacturing processes associated with th prostheses (Eckert K.L., Herstellung von kleinen Mitt lohrimplantaten für Tierversuche an Kaninchen. Profe sur für Biokompatible Werkstoffe und Bauweise ETH Zürich. Personal communication. September 1 1999). In essence, a preformed shaft was sintered a pressed together with a silt mass (representing the hea contained within a mold. As a result, a secondary ur form structure was produced. Hence, the weake structural point was primarily concentrated in the vicini of the prosthesis head/shaft interface, as evidenced by th results.

The evaluation of structural integrity was accurate determined as a result of the precision of the wet grindi technique used. Compared with the sawing microton method used by other researchers, which only allows f a limited number of specimen sections (approximate three) ranging between 30–80 μm in width, the grindi technique permits the implant to be viewed in its entire (controlled wearing of the specimen surface; 1 μ range). Had it not been for the meticulous grinding of th specimens, implant fissures and perforations may ha been overlooked in their entirety. The authors recor mend that the conventional sawing microtome techniq be thoroughly scrutinized when planning for future e perimental trials involving the collection of morpholog data associated with middle ear implant materials.

Functionality

Titanium has long been favored in middle ear surgery because of its minimal weight. This attribute makes the metal suitable for conducting sound waves in the high frequency range (10,17,18,27). Several clinical follow-up studies examining various tympanoplastic procedures have reported promising results involving middle ear prostheses constructed of commercially pure titanium. After a postoperative period of 1.5 years, a residual air–bone gap of 0–35 dB was recorded for patients who had received titanium implants (23,27). In a retrospective study, the implantation of titanium prostheses (tympanoplasty type III) was analyzed in 528 patients (22). The patients' healiug results and hearing gains were subjected to evaluation during a period of 6 months after implantation. Only 4.4% of the prostheses were rejected. Use of the titanium TORP model proved successful based on the audiological results. An average hearing gain of 15–20 dB was achieved in a frequency range between 0.5 and 6 kHz. Interestingly, the hearing gain continually increased over a period of 6 months. Eleven of the implanted patients' ears demonstrated granulation within the implantation area, which was reduced to three cases after a period of 6 months.

Stupp et al. (26) also reported on the functional data regarding titanium TORPs and PORPs. Their study included 582 patients suffering from chronic middle ear disease. After implantation, the hearing results were followed up for a period of up to 3 years (average follow-up time, 11.7 mo). Again, the individual air–bone gaps were measured for frequencies lying in the 0.5–4 kHz range. A reduction in the air–bone gap was recorded in 72% of the cases. The continual closure of the air–bone gap was calculated over a period of 30 months. Poor hearing results were based on dislocation, recurrence of chronic middle ear disease, and hypertrophic scar tissue fixation of the prostheses. Adverse reactions of the implants were not noted. In 79.4% of the cases, otoscopic results revealed no signs of middle ear mucosa inflammation or destruction of the tympanic membrane. Prosthesis extrusion was noted to be dependent on the degree of tubal insufficiency and the status of tympanic cavity aeration.

Promising results were also reported for Al_2O_3. Clinical follow-up studies indicated that the average increase in the hearing thresholds for both Al_2O_3 TORPs and PORPs remained under 20 dB (56). These results were recorded after 6 years of implantation. Hearing via air conduction had remained stable. It was thus assumed that prosthesis function was not influenced by dislocation, nor limited by scar tissue. Zöllner and Strutz (35) reported clinical trials involving Al_2O_3 prostheses that were implanted in patients suffering from chronic middle ear disease. The study demonstrated that patients with poorly ventilated tympanic cavities and retracted eardrums benefited from implanted Al_2O_3 prostheses with cartilage overlays between the drum and the prosthesis head. The extrusion rates were thus reduced from 16% to 5%. Within a frequency range of 0.5–2 kHz, a majority of the ears examined demonstrated a residual air–bone gap of less than 20 dB. However, it was also discovered that scar tissue contractions were capable of displacing the implants away from the overlying cartilage discs. This resulted in extrusion of the prostheses.

After reviewing the results of this study, it would be advisable to investigate the functionality of porous oxide ceramics more critically in the future. Although a continual increase in conductive hearing loss was not observed during the 300 day trial period—thereby demonstrating the success of the ossiculoplastic reconstruction technique (42)—the morphologic development of the TORPs show that long-term stability and functionality are not promising. Given a longer implantation period, it is speculated that conductive hearing would begin to further deteriorate. Therefore, it should be taken into consideration that perhaps functionality alone is not an adequate method of evaluation when it comes to judging the performance of ossicular replacement materials. The morphologic development of the prosthesis in situ dictates the loug-term outcome associated with implant functionality. Hence, the authors suggest that long-term observations of implanted alloplastic materials should involve a period of at least 3 years, during which emphasis should be placed on morphologic analysis under normal and inflamed conditions within the tympanic cavity. Although several types of alloplastic materials in the form of a PORP or TORP demonstrated promising audiological results in the past, it must be understood that these results were primarily based on proper implant placement, design, and weight. These factors are, however, only relevant if the implant material demonstrates long-term biocompatibility. In other words, if improper material selection compromises the structural integrity of a prosthesis, then long-term functionality is predestined to failure regardless of the initial results. Thus, morphologic development cannot be ignored and short-term functional results based on audiometric testing alone cannot be used as a standard when evaluating ossicular replacement performance.

Most of the current literature in circulation reports of morphologic trial times between 12 to 18 months. Functional results are usually restricted to a maximum of 2 to 3 years. The authors recommend that these relatively short trial times be lengthened to appropriately evaluate the biocompatibility of all alloplastic middle ear prostheses.

CONCLUSION

Based on the changes in morphology observed in the oxide ceramic implants during the course of the 300-day experimental trial period, the following suggestions regarding material content and manufacturing should be taken into consideration. First, titanium, in its constellation as an oxide ceramic, appears to be superior to its aluminum counterpart. This was evident after examination of the tympanic cavity. The encapsulated aggregates found in association with the perforated Al_2O_3 shafts prompted a cause for concern. It is most likely that traces of Al_2O_3 can be found accumulating in these structures.

The continual increase in the concentration of aluminum ions found in the extracellular matrix could have serious repercussions on the physical condition of an organism. This becomes relevant on acknowledgment of the possible toxicity associated with the metal. Secondly, it is important that TiO_2 ceramics be sintered from a uniform mold; that is, a manufacturing process which begins with a solitary mixture and results in a single product. This would hinder the tendency to develop fissure formations at structurally weak junctional points.

In addition, the effect of surface topography in the form of porosity is an aspect of significant importance. To increase ceramic material density, the pores must be reduced in size and frequency. This has a positive effect on material stability and integrity. Consequently, fracturing and dissolution can be avoided. Hence, the smaller the pore size, the better the long-term results of the implants because of their increased resistance against oscillatory stress. Reduced porosity also allows for controlled osseointegration, an advantageous characteristic associated with improved sound conductibility. Perhaps the answers to the problems associated with selecting an ideal alloplastic material for ossiculoplasty lie in the nanophase TiO_2 ceramics.

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