



## Anti-infective and osteointegration properties of silicon nitride, poly(ether ether ketone), and titanium implants

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### ABSTRACT

Silicon nitride ( $\text{Si}_3\text{N}_4$ ) is an industrial ceramic used in spinal fusion and maxillofacial reconstruction. Maximizing bone formation and minimizing bacterial infection are desirable attributes in orthopedic implants designed to adhere to living bone. This study has compared these attributes of  $\text{Si}_3\text{N}_4$  implants with implants made from two other orthopedic biomaterials, i.e. poly(ether ether ketone) (PEEK) and titanium (Ti). Dense implants made of  $\text{Si}_3\text{N}_4$ , PEEK, or Ti were surgically implanted into matching rat calvarial defects. Bacterial infection was induced with an injection of  $1 \times 10^4$  *Staphylococcus epidermidis*. Control animals received saline only. On 3, 7, and 14 days, and 3 months post-surgery four rats per time period and material were killed, and calvariae were examined to quantify new bone formation and the presence or absence of bacteria. Quantitative evaluation of osteointegration to adjacent bone was done by measuring the resistance to implant push-out ( $n = 8$  rats each for Ti and PEEK, and  $n = 16$  rats for  $\text{Si}_3\text{N}_4$ ). Three months after surgery in the absence of bacterial injection new bone formation around  $\text{Si}_3\text{N}_4$  was  $\sim 69\%$ , compared with 24% and 36% for PEEK and Ti, respectively. In the presence of bacteria new bone formation for  $\text{Si}_3\text{N}_4$ , Ti, and PEEK was 41%, 26%, and 21%, respectively. Live bacteria were identified around PEEK (88%) and Ti (21%) implants, whereas none were present adjacent to  $\text{Si}_3\text{N}_4$ . Push-out strength testing demonstrated statistically superior bone growth onto  $\text{Si}_3\text{N}_4$  compared with Ti and PEEK.  $\text{Si}_3\text{N}_4$  bioceramic implants demonstrated superior new bone formation and resistance to bacterial infection compared with Ti and PEEK.

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### 1. Introduction

Silicon nitride ( $\text{Si}_3\text{N}_4$ ) is a synthetic non-oxide ceramic that is used in many industrial applications, and has been investigated or adapted as a biomedical material since 1989 [1–14]. The rationale for using  $\text{Si}_3\text{N}_4$ -based implants in skeletal reconstruction is based on its favorable combination of mechanical strength, microstructure, and cytotoxicity [11,12,15]. Polished and porous implants made of  $\text{Si}_3\text{N}_4$  have shown encouraging outcomes in spine and maxillofacial surgery [11,13]. In contrast to the limited clinical experience with  $\text{Si}_3\text{N}_4$ , implants made of titanium (Ti) and its alloys have been used in skeletal reconstruction for many decades [16,17]. More recently, poly(ether ether ketone) (PEEK), a polymer with modest strength and a low modulus of elasticity compared with metal, has been investigated as an orthopedic biomaterial [18,19] and is commonly used in spine surgery [20].

Long-term, stable fixation of orthopedic implants to skeletal bone relies on direct in-growth of host bone into the textured implant surface. Implant failure and clinical symptoms of pain can follow if such bone in-growth does not occur. A serious problem that can complicate an otherwise well-fixed and properly functioning implant is bacterial infection, which can manifest itself immediately after surgery or even years later. Implant-related infections usually require extensive surgical debridement, implant extraction, and prolonged antibiotic treatment [21,22]. Implant surfaces can accumulate serum proteins that can promote bacterial adhesion and colonization [23]. Adherent bacteria such as *Staphylococcus epidermidis* are known to synthesize a complex surrounding biofilm layer that is impervious to host immune surveillance and systemic antibiotic therapy [23–25]. Therefore, resistance to bacterial infection would be a very desirable material property in orthopedic implants. To date, however, all implant materials are susceptible to bacterial seeding in vivo.

The purpose of this investigation was to test the potential antimicrobial properties and osteointegration capability of dense  $\text{Si}_3\text{N}_4$  implants in an animal model. For comparison we used two common

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**Table 1**  
Comparative properties of medical grades of Si<sub>3</sub>N<sub>4</sub>, ASTM grade 4 titanium and Invibio PEEK Optima®.

Property	Units	Si <sub>3</sub> N <sub>4</sub>	Ti – ASTM Grade 4	PEEK Optima®
Composition	NA	Si <sub>3</sub> N <sub>4</sub> , Y <sub>2</sub> O <sub>3</sub> , Al <sub>2</sub> O <sub>3</sub>	Chemically Pure	Chemically Pure
Surface Composition	NA	SiNH <sub>2</sub> and SiOH	TiO <sub>2</sub> Layer	–OH Groups
Surface Roughness (AFM)	nm	25.3	3.06	1
Isoelectric Point	NA	9	~4.5	~4.5
Surface Charge at pH = 7	NA	Positive	Negative	Negative
Sessile Water Drop Wetting Angle	Degrees	39	76	95

orthopedic biomaterials, Ti and PEEK. The null hypothesis was that Si<sub>3</sub>N<sub>4</sub>, Ti, and PEEK would demonstrate identical properties in terms of bacterial infection and bone growth onto implant surfaces.

## 2. Materials and methods

### 2.1. Biomaterials

The materials used in this study included medical grades of Si<sub>3</sub>N<sub>4</sub> (Amedica Corp., Salt Lake City, UT), ASTM grade 4 titanium (Fisher Scientific, Continental Steel & Tube Co., Fort Lauderdale, FL) and PEEK Optima® (Invibio, Thornton Cleveleys, UK). The Si<sub>3</sub>N<sub>4</sub> provided by Amedica was produced using sintering with hot isostatic pressing with Al<sub>2</sub>O<sub>3</sub> and Y<sub>2</sub>O<sub>3</sub> as densification additives, similar to methods previously reported by Iturriza et al. [26]. All samples were sterilized using ultraviolet light exposure for 24 h on all sides. The relevant properties of these three materials are given in Table 1.

The surfaces of the three materials were characterized for morphology and roughness by scanning electron microscopy (SEM) using a LEO 1530 VP FE-4800 field emission gun scanning electron microscope (Zeiss, Peabody, MA). The results are shown in Fig. 1. All three materials were used in the as-received condition. The PEEK and medical grade Ti samples had machined surfaces, whereas the Si<sub>3</sub>N<sub>4</sub> ceramic was as-fired. SEM images of PEEK and Ti reveal a macro-rough surface typical of machined components. However, the as-fired Si<sub>3</sub>N<sub>4</sub> implant material possessed nanostructured surface features with a larger total surface area compared with Ti and PEEK. Sessile water drop tests using a Krüss Easy Drop Contact Angle instrument (Germany) with analysis by the Drop Shape Analysis program (v.1.8) were performed on each material to assess their wetting characteristics (Table 1) [27].

### 2.2. Calvarial defect model

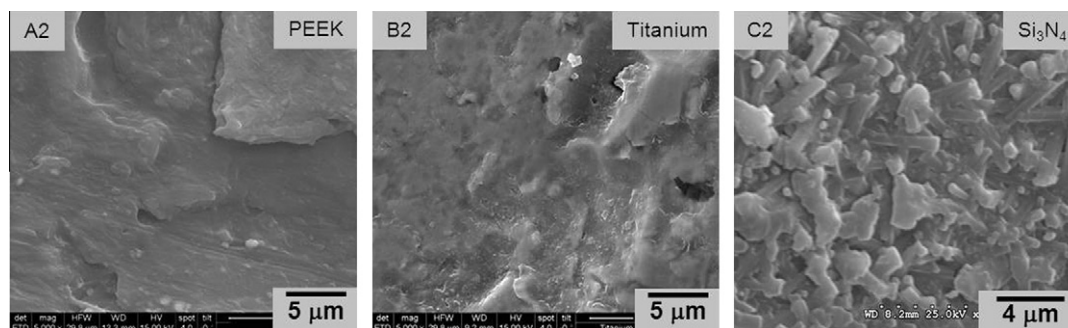
Ninety six skeletally mature Wistar rats (350–450 g) underwent treatment using an experimental protocol that was approved by the Institutional Animal Care and Use Committee. Animals were housed and cared for in accordance with standard guidelines in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, according to the policies and principles

established by the Animal Welfare Act and the NIH Guide for Care and Use of Laboratory Animals. Prior to surgery the animals were administered atropine sulfate (0.05 mg kg<sup>-1</sup> subcutaneously) 15–30 min before induction of anesthesia using ketamine (40–80 mg kg<sup>-1</sup> intraperitoneally). All surgery was performed under aseptic conditions, with a sterile surgical field, surgical gown, cap, mask, sterile gloves, and sterile instruments. Immediately prior to surgery the surgical site was shaved and disinfected topically with Betadine scrubs. Using magnification and high intensity illumination a full thickness incision was made from the nasofrontal area to the external occipital protuberance along the mid-sagittal plane, permitting reflection and exposure of the calvarium. Under constant copious irrigation with saline a trephine bur was used to create critical sized elliptical through-and-through defects in the parietal bones, measuring larger than the 10 × 10 × 1.75 mm implants [28]. Trephined bone was carefully removed to avoid injury to the underlying dura.

Defects were randomly reconstituted with test coupons of either Ti (n = 24), or PEEK (n = 24), or Si<sub>3</sub>N<sub>4</sub> (n = 48). Prior to closure the surgical site in half of the animals receiving each biomaterial was randomly inoculated with a standard aliquot of 1 × 10<sup>4</sup> *S. epidermidis* (ATCC, Manassas, VA, strain no. 35984). The other half received a matching aliquot of saline as a control. After surgical repair of the wound the animals were individually caged under a warming lamp and intermittently turned from side to side. The animals were administered buprenorphine (0.02 mg kg<sup>-1</sup> intramuscularly) as an analgesic for 3–5 days post-operatively. The surgical sites were monitored daily for untoward swelling or signs of infection. At least three animals (for each biomaterial and bacteria/saline group) were killed at 3, 7, and 14 days, and 3 months post-surgery via CO<sub>2</sub> administration and cervical dislocation.

### 2.3. Specimen preparation

Block sections of the calvarium were harvested from the surgical sites and fixed in 10% neutral buffered formalin. After exposing the area the calvarium was resected with a high-speed handpiece. A thin layer of cerebral tissue was excised with a scalpel. The remaining tissue was left attached to the inner face of the cranium in order to prevent damage to the implantation area. Upon receipt



**Fig. 1.** SEM surface microstructures of PEEK Optima®, titanium and silicon nitride.

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