Surface Chemistry of a Silicon Nitride Bioceramic Enhances Spinal Fusion: A Case Study

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INTRODUCTION: With the exception of synthetic hydroxyapatite (HAp), most bioceramics are considered to be bioinert. They neither participate in the healing process nor create added comorbidities. While HAp is known to accelerate bone healing, its use is limited to non-structural applications because of its poor mechanical properties. Conversely, silicon nitride (Si_3N_4), a relatively new bioceramic, not only provides high mechanical integrity, but also shows pronounced *in vitro* osteoconductivity.[1,2] Since 2008, it has been utilized as an interbody device in spinal fusion surgery. This case study presents the first detailed physical, chemical, and spectroscopic analyses of a retrieved Si_3N_4 implant from a human patient after ~11 months of *in vivo* service. Results were compared to a similarly retrieved polyetheretherketone (PEEK) implant obtained after being *in vivo* for ~14 months. It was found that Si_3N_4 enhanced bone reformation via the release of silicon and nitrogen ions from its surface which were endocytotically acquired by mature osteoblasts and subsequently incorporated into new native hydroxyapatite resulting in enhanced osteointegration. In contrast, native bone adjacent to the PEEK device showed no chemical changes and a lower propensity for osteogenic activity.

METHODS: The Si_3N_4 implant, a cervical device (16 x 12 x 8 mm, Amedica Corp., Salt Lake City, UT, USA), was retrieved from a 58 year-old male patient after ~11 months *in vivo* due to an anatomical change requiring removal of the accompanying metallic cervical plate. For comparison, a lumbar PEEK implant (10 x 26 x 12 mm; Amedica Corp.) was retrieved from a 60 year-old male patient ~14 months after implantation due to non-union. Both implants were subjected to careful dehydration, staining, and histomorphometric analyses. Confocal Raman spectroscopy was conducted on each implant using a 532 nm Ar-ion laser operating at 100 mW (T-64000, Jobin-Yvon/Horiba Group, Kyoto, Japan) coupled with a nitrogen-cooled 1024 x 256 pixels CCD camera (CCD-3500V, Horiba Ltd., Kyoto, Japan). A He-Ne lamp was employed for all measurements as an internal reference for Raman peak positions. Raman band parameters were obtained by fitting the raw experimental spectra to mixed Lorentzian-Gaussian curves. X-ray photoelectron spectroscopy (XPS, Axis Ultra, Manchester, UK) was also performed using Al-k_α radiation at pass energies of 160 and 40 eV, providing chemical resolutions of ~0.1 and 0.01 atomic percent (at.%), respectively. Lastly, Fourier Transform Infrared Spectroscopy (FT-IR) was conducted using an imaging system (Spotlight 200, Perkin Elmer, Waltham, MA, USA). FT-IR spectra were acquired at aperture size of 200×200 μm^2.

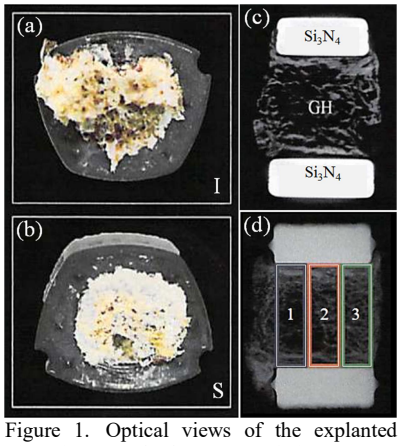

Figure 1. Optical views of the explanted Si_3N_4 intervertebral spacer: Inferior (a), Superior (b), Micro-CT image (c), and Microradiograph (d). In the latter analysis, the analyzed area was divided into three longitudinal sectors for histomorphometric analyses.

RESULTS: Optical, micro-CT, and micro-radiographic images of the Si_3N_4 implant are shown in Fig. 1(a)~(d). From the histological analyses, markedly different bone apposition indices were obtained for the Si_3N_4 and PEEK implants (*i.e.*, 19.12 ± 11.49% and 4.41 ± 9.09%, respectively). Bone volumes within the graft hole were also dissimilar, with the Si_3N_4 device showing a range of 12.63% (sector 1) to 74.47% (sector 3), while the PEEK implant's range was between 0.00% and 31.83%. Raman spectroscopy scans across the graft hole for the Si_3N_4 implant are shown in Fig. 2(a), with the corresponding intensity and position for the P-O stretching band of hydroxyapatite (~960 cm^{-1}) at each scan location provided in Fig. 2(b). Note that this band was significantly shifted to lower frequencies and broadened at locations close to the implant's surface. Upon deconvolution of the shifted bands, it was determined that silicon ions were substitutionally incorporated into the native hydroxyapatite's crystal structure in place of phosphorus. XPS and FT-IR analyses (not shown) confirmed not only the inclusion of silicon into hydroxyapatite, but also the incorporation of nitrogen. Conversely, Raman, XPS, and FT-IR scans of the graft hole for the PEEK implant did not detect any substitutional ions or structural changes.

DISCUSSION: Three independent spectroscopic probes were used to analyze two short-term retrievals – Si_3N_4 and PEEK. The comparative data demonstrated that the surface chemistry Si_3N_4 played an active role in enhancing osteogenesis within the graft hole. Si_3N_4 reacted with biological fluids to form minute amounts of orthosilicic acid ($Si(OH)_4$) and ammonia (NH_3). In turn, these compounds were endocytotically scavenged by osteoblasts and subsequently deposited in the newly formed bone. The combined spectroscopic analyses indicated that SiO_4^{4-} entered the hydroxyapatite structure substitutionally for PO_4^{3-}, whereas nitrogen anions (which were found to be bonded to calcium cations) were substituted for oxygen in the PO_4^{3-} and SiO_4^{4-} tetrahedra as well as OH groups. While it is commonly known that silicon is essential for bone health,[3] this case study represents early evidence that both silicon *and* nitrogen are effective in enhancing osteogenesis.

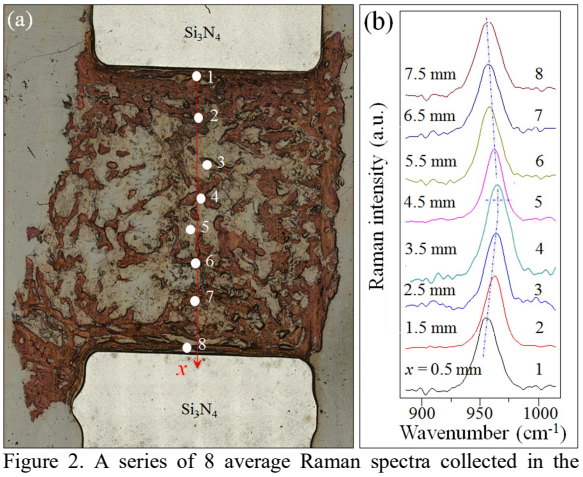

Figure 2. A series of 8 average Raman spectra collected in the Si_3N_4 spinal explant at the locations labeled 1~8 (a); and, the Raman band for P-O stretching in hydroxyapatite as a function of these 8 locations (b).

SIGNIFICANCE: Biomaterials which actively facilitate bone healing represent an important therapeutic advancement for spinal fusion devices. In contrast to traditional bioinert compounds (*i.e.*, PEEK), solid Si_3N_4 may provide local healing comparable to synthetic hydroxyapatite and anti-resorptive drugs.

REFERENCES: [1] G. Pezzotti, *et al*., *ACS Biomater. Sci. Eng.,* **2**, [7], 1121-1134, (2016); [2]G. Pezzotti, *et al*., *Sci. Rept*., **6**, 31717, (2016); [3]R. Jugdaohsingh, *J. Nutr. Heal. Aging*, **11**, [2], 99-110, (2007).