**Surface Characterization of a Bioactive Composite: Theory for Mechanism of Action of Bone Bonding**

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**Statement of Purpose:** Bioactive glasses have been investigated since the 1970s as biomaterials that evoke a bone bonding response when implanted in a bony site.[1] This phenomenon has been studied *in vitro* by many investigators to elucidate the mechanism of action for the *in vivo* response.[1] A novel biomaterial incorporating a bioactive glass-ceramic, Cortoss® (Orthovita, Inc., Malvern, PA), has been characterized through *in vitro* and *in vivo* studies to understand the bioactivity of this material. Cortoss has been engineered specifically for use in orthopedic procedures and offers a unique alternative to existing polymethylmethacrylate (PMMA) cements. The ability for Cortoss to directly bond to host bone provides an advantage with respect to material integration and mechanical stability after implantation. An FDA approved IDE clinical trial on this material is currently underway.

**Methods:** Cortoss was investigated *in vitro* according to the methods of Kokubo et al. using Simulated Body Fluid (SFB) for a period of up to 14 days at 37°C. Samples were analyzed using Scanning Electron Microscopy (SEM), Energy Dispersive Spectroscopy (EDS), and Fourier Transform Infrared Spectroscopy (FTIR) to evaluate calcium phosphate (CaP) formation. Preclinical studies were conducted in a rabbit tibial defect model to confirm bone bonding. Histology of material implanted in a vertebral body was also examined.

**Results:** Results from day 14 of the *in vitro* SBF study can be seen in Figure 1. Backscattered SEM imaging (BSE) showed calcium phosphate growth as early as day one which progressed to cover the entire material surface by day three. At day 14 the growth of this layer had progressed and the presence of calcium phosphate was confirmed through elemental EDS analysis and FTIR.

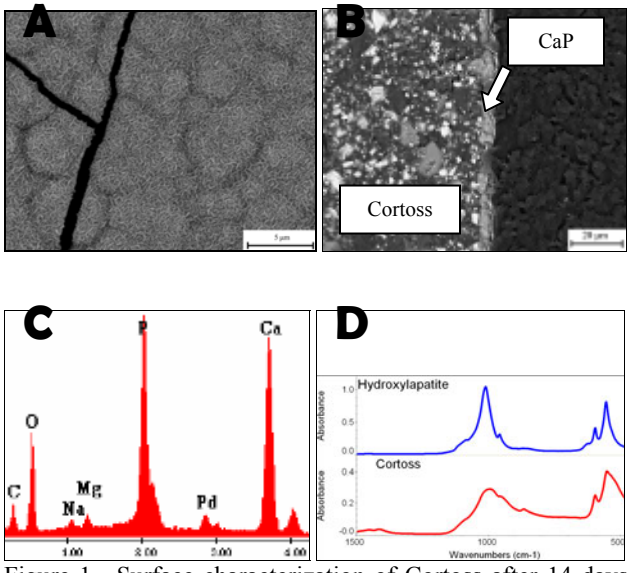


Figure 1. Surface characterization of Cortoss after 14 days of immersion in SBF. BSE images of the (A) surface and (B) cross section, as well as (C) EDS and (D) FTIR spectra confirm the growth of a surface calcium phosphate (CaP) layer.

The results of *in vivo* studies support the notion of a surface mediated cellular response as evidenced by the histology presented in Figure 2. Direct bone bonding at the material interface is seen after implantation for 8 weeks in a rabbit tibial defect and 5 months in a human vertebra. This phenomenon is not observed with commercially available PMMA cements, where instead a fibrous tissue layer intervenes between the material surface and the surrounding bone.

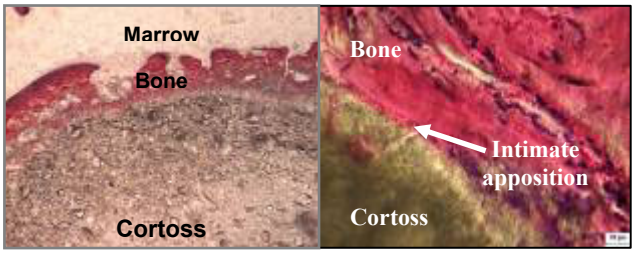


Figure 2. Cortoss histology (H&E stain). Intimate bony apposition can be seen in material that has been implanted in a rabbit medullary defect for 8 weeks (left, 20x) and a human vertebral body for 5 months (right, 50x).

**Discussion:** *In vitro* bioactivity is initiated by the release of sodium from the glass-ceramic, resulting in a localized alkaline environment. An intermediate silica rich gel layer then forms, promoting the deposition of calcium and phosphorous from solution onto the material surface. The *in vivo* response involves osteoblast attachment with subsequent collagen matrix production that becomes bone. This osteoblast attachment is likely mediated by the kinetics of the reaction at the material surface. It has been reported in the literature that bone formation and bonding occurs *in vivo* when calcium phosphate formation occurs within 3 days *in vitro*.[2] Initially following implantation, the relatively hydrophilic nature of Cortoss (with respect to PMMA cements) as well as the negatively charged surface may be hindering the adsorption of negatively charged plasma proteins. Hydrophobic materials such as PMMA, however, are likely promoting surface fouling via the adsorption of these proteins which encourages fibroblast attachment and subsequent fibrous tissue encapsulation. Studies are underway to investigate the hypothesis of a hydrophilic, negatively charged ($Si\text{-}O^-$) interface creating a non-fouling surface as a bridge to osteoblast attachment.

**Conclusions:** By encouraging the rapid incorporation of calcium phosphate, a surface favorable to osteoblast attachment is formed at the Cortoss material interface. This bioactive mechanism of action promotes adjacent bone formation and direct bone apposition to the material surface when implanted *in vivo*, providing a unique advantage over PMMA cements for use in orthopedic procedures.

**References:** [1] Kokubo T. Biomat. 2006; 27:2907-2915. [2] Fujibayashi S. Biomat. 2003; 24:1349-1356.