Osseointegration and Biocompatibility Evaluation of Silicon Nitride Composite Using Ovine Distal Femoral Epiphyseal Insertion and Rabbit Paravertebral Muscle Implantation Models

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INTRODUCTION: Silicon nitride (Si_3N_4) is a non-oxide abiotic ceramic biomaterial that was originally developed in the early 1980s. In addition to its strength, stability and appealing imaging properties such as partial radiolucency, the surface chemistry of Si_3N_4 is hypothesized to be conducive to osteogenesis, have anti-infective properties, and to increase bone-to-implant contact, resulting in improved osseointegration [1,2]. Because of this unique combination of material properties, Si_3N_4 can be used for spinal fusion implants and is being considered for bearing components in prosthetic hip and knee joints. In this development program, an osseointegration study evaluated the ingrowth capability of Si_3N_4 materials implanted into the femoral condyles of skeletally mature sheep compared to similar titanium controls. A concurrent ectopic bone formation study was designed to evaluate the heterotopic bone formation potential of a particularly bioactive form of porous Si_3N_4 compared to titanium alloy implants in non-osseous sites, utilizing implantation in rabbit paravertebral muscles.

METHODS: In the first study, eight (8) skeletally mature female sheep (Dorset Rideau Arcott Hybrids) were used in order to evaluate two types of porous metallic dowels (N_2-annealed Si_3N_4 *vs.* Ti-6Al-4V cylindrical implants; n=8 samples per test and control group; 11.2-mm ⌀ × 24.13-mm L; 72% circular central porosity; 25% circular area corresponding to solid shell) were inserted in a press-fit fashion, bilaterally into ovine femoral medial condyles following defect creations. The specific objective was to quantify bone ingrowth and remodeling phenomena using histomorphometry and histopathology following four (4) weeks (28 ± 2 days) and twelve (12) weeks (84 ± 5 days) of implantation. In the second study, the osteoinductivity potential of the corresponding biomaterials cylindrical implants (discs, 6-mm ⌀ × 3-mm thickness) were implanted bilaterally in four (4) paravertebral muscle pouches of two (2) New Zealand White rabbits for a period of eight (8) weeks (56 ± 3 days) of implantation. The specific objectives were to evaluate ectopic bone formation (if any) and other local effects using histomorphology and histopathology analysis at 8 weeks (56 days ± 3 days) post-implantation. All surgical procedures and animal husbandry adhered to protocols approved by the Institutional Animal Care and Use Committee of an AAALAC-certified preclinical testing facility. Upon receipt and before use in this study, all animals were held for environmental acclimation for at least seven (7) days. All cages and enclosures conformed to standards set forth in the NIH Guide for Care and Use of Laboratory Animals.

RESULTS: The Si_3N_4 condylar implant showed good osteoconductivity and histomorphometry results (Fig. 1). The mean maximal linear penetration of new bone formation within the implant was higher in the Si_3N_4 test articles than in the porous Ti controls at both 4 and 12 weeks. The muscle implantation study revealed that implants made of porous Si_3N_4 and titanium alloy (controls) exhibited excellent safety and biocompatibility as evidenced by the mild tissue reaction without obvious adverse effects. Ectopic bone formation/osteoinductivity was not seen around the paravertebral devices or within the pores of the devices. Nevertheless, good neovascularization, characterized by minimal focal capillary proliferation or groups of 4 to 7 capillaries, was observed in the fibrous connective tissue/fibrosis around the device and within the device pores. Neovascularization scores were similar in both groups.

DISCUSSION: A new non-oxide ceramic material, silicon nitride (Si_3N_4), has demonstrated favorable osteoconductivity in this study. Unlike synthetic apatites, it has the strength and stability to be used in structural applications. It has yet to be effectively evaluated as to its osteoinductive behavior although it is believed that the surface chemistry of Si_3N_4 may also be conducive to osteogenesis. These two studies have contributed to evaluate a particularly active form of Si_3N_4 in terms of its ability to conduct and generate new bone formation within its porous structure.

SIGNIFICANCE/CLINICAL RELEVANCE: Novel Si_3N_4 composites, unlike synthetic apatites, are considered to have the strength, stability as well as partial radiolucency to be used in structural applications. Their porous core allows for osteoconduction, resulting in an improved osseointegration, which may contribute to reduce the need for bone grafting.

REFERENCES: [1] M.C. Anderson *et al*. Bone ingrowth into porous silicon nitride. J Biomed Mater Res A. 2010; 92(4):1598-1560. [2] T.J. Webster *et al*. Anti-infective and osteointegration properties of silicon nitride, poly(ether ether ketone), and titanium implants. Acta Biomater 2012; 8(12):4447-4454.

IMAGES:

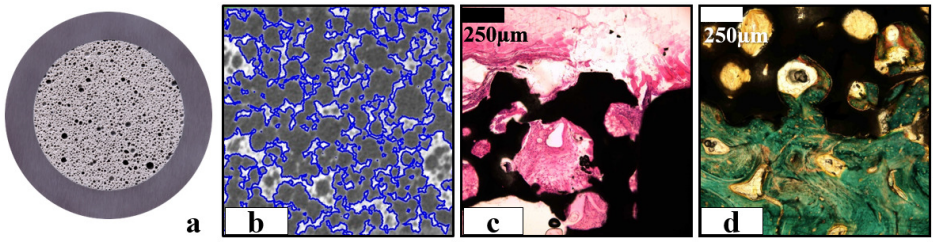

Figure 1. Si_3N_4 implant cross-section view under (a) high-resolution radiography and (b) micro-computed tomography. Light microscopy view of Exakt-microground longitudinal Si_3N_4 sections of: (c) rabbit paravertebral muscular tissue integration at 8 weeks postop (H&E, 10x) and (d) osseointegration after 12 weeks in a ovine medial condyle (Goldner's Trichrome, 10x) showing pores colonized with mineralized bone.