Local Tissue Response and Bone Ingrowth into Titanium Nitride-Coated 3D-Printed Porous Titanium Structures in a Canine Model

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INTRODUCTION: Titanium and its alloys are materials that have been used successfully in orthopedic implants due to their excellent biocompatibility, high corrosion resistance, high toughness, and low density[1]. Currently available titanium porous structures made with 3-D printing techniques have been shown to allow significant bone growth into the implant, yielding clinically acceptable osseointegration in animal models[2]. However, titanium and its alloys are more susceptible to wear, making untreated titanium a non-ideal candidate for articulating surfaces[1]. Titanium Nitride (TiN) when used as a coating offers increased wear resistance compared to uncoated titanium implants[1]. Despite demonstrated clinical success of TiN-coated porous titanium structures[3], the local tissue responses including inflammation remain to be further evaluated *in vivo*. This canine implantation study investigates the local tissue responses including inflammation, and osseointegrative capabilities of TiN-coated porous surface of titanium implant made using different 3-D printing technologies.

METHODS: Twelve skeletally mature male mongrel canines (25-35kg; 12-17 months) were used in the study: six were randomly selected for each of 28-day and 84-day timepoints. Male canines were selected to avoid any conflicting findings related to hormonal differences. Fully porous cylinder plug implants (5mm diameter, 10mm length) were manufactured using the following 3-D printing techniques: Laser Rapid Manufacturing (LRM) or Electron Beam Melting (EBM). For each manufacturing technique, the plugs either remained uncoated or coated with TiN, resulting in four groups: LRM, LRM-TiN, EBM, and EBM-TiN, with LRM used as the predicate control based on its successful clinical history. Each femoral diaphysis was implanted with four implants (one from each treatment group) using a transcortical model. At scheduled sacrifice, explants from the left femurs were collected, fixed in 10% neutral buffered formalin, embedded in PMMA, prepped for undecalcified histology, and stained with Hematoxylin and Eosin (H&E). Slides were blinded and scored following the Annex E of ISO 10993-6[4] with additional parameters added for full evaluation of the healing response. Bone ingrowth (BI) was graded using the following semi-quantitative system: 0=no ingrowth, 1=1-10% ingrowth, 2=11-25% ingrowth, 3=26- 50% ingrowth, 4=51-75% ingrowth, 5=76-100% bone ingrowth. All surgical procedures and animal husbandry adhered to protocols approved by the IACUC of an AAALAC- and CCAC-accredited preclinical facility.

RESULTS: At all timepoints and treatment groups, the biocompatibility response was ideal with low inflammation (scores of 1, Fig. 1A,B). Fibrosis typically scored 1 (narrow band, Fig. 1C) and rarely 2 (moderately thick band, Fig. 1D), while neovascularization was scored as 1 (minimal capillary proliferation, focal, 1-3 buds) and only occurred when fibrosis was present. BI was greater in EBM and EBM-TiN samples (score of 4.5) compared to LRM-TiN and LRM (scores of 3.7 and 2.7, respectively) at 28 days. By 84 days, all groups exhibited similar outcomes, with EBM and EBM-TiN scoring 5.0, and LRM and LRM-TiN scoring 4.8, indicating significant bone ingrowth and integration of new bone within the porous implants in all four groups (Fig. 2).

DISCUSSION: The histological evaluation showed that all four groups are compatible with the host tissue, indicating the TiN coating has no significant impact on biological response in comparison to uncoated Ti alloy. Osseointegration was significant and similar in all four implant groups, providing evidence that the presence of TiN coating does not negatively impact osseointegration of the implant.

SIGNIFICANCE/CLINICAL RELEVANCE: This study shows that the addition of TiN coating has no significant effect on osseointegration into the implant and does not elicit an adverse inflammatory or immune response in canines. This provides additional insight into the inflammatory mechanisms and osseointegrative response of TiN coatings to native tissue in canines. Furthermore, this canine study demonstrated that both TiN coated and uncoated 3-D printed porous structures are substantially equivalent with respect to osseointegration and local tissue responses.

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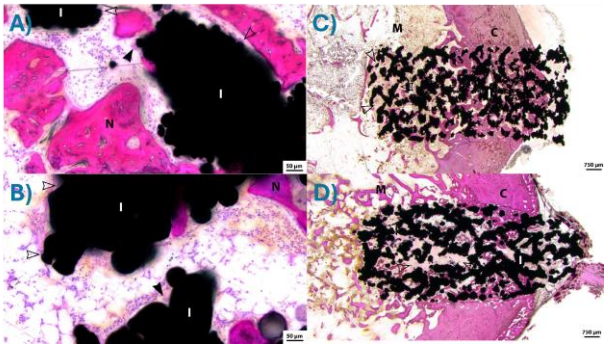

Figure 1: Representative H&E images showing inflammatory and tissue response at 28 (A) and 84 (B) day time points. Both exhibit low inflammation, with low numbers of macrophages lining the implant surface (open arrowheads) and occasional multinucleated giant cells (closed arrowheads). Representative H&E images showing fibrosis scores of 1 (C) and 2 (D), in open arrowheads. For A-D, N = new bone growth into implant, I = porous implant, C = cortical region, M = medullary region

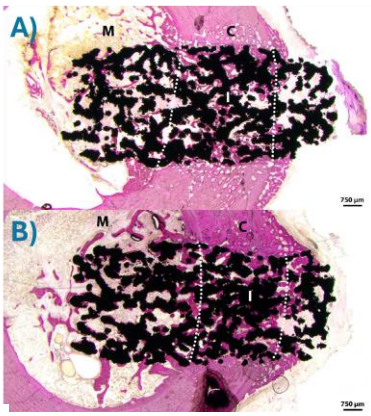

Figure 2: Representative images showing bone ingrowth at 28 days (A), showing a score of 2 in the medullary region (11-25%) and a score of 3 (26-50% ingrowth) in the cortical region. By 84 days (B), scores have increased to 3 in the medullary region (26-50%) and 5 in the cortical region (76-100%)