

Methods to Quantify *in vivo* Osseointegration of Porous Metallic Implants

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INTRODUCTION: Bone attachment of metallic implants in orthopedics can be achieved through either cemented fixation or cementless biological fixation. In biological fixation, a porous structure on the implant's bone-contacting surfaces enables bone tissue to grow into the pores over time, creating a strong mechanical interlock for stable long-term fixation. The growing use of biological fixation, driven by the fast advancement in additive manufacturing technologies, emphasizes the importance of effective osseointegration in metallic implants. Preclinical animal models (e.g., sheep, rabbit) are often used to assess *in vivo* osseointegration performance of porous implants by observing bone tissue ingrowth at the bone-implant interface over time. When quantifying osseointegration on histomorphometric images of the bone-implant interface, various methods can be used. A commonly used parameter in literature is called "Bone in Available Void" (BIAV), which is defined as the percentage of bone area within the total available void area in a histomorphometry image [1-4]. While useful for comparing similar porous structures, BIAV has limitations for dissimilar implants, as implants with lower porosity may yield higher BIAV ratios, leading to biased results. This study aimed to: 1) demonstrate that BIAV may yield biased results when comparing implants with different porous structures; and 2) propose an alternative metric that could be more robust and clinically relevant.

METHODS: Osseointegration of two types of porous titanium implants was evaluated using an established ovine model (*Ovis aries* sheep) [1-4]. The implants included a laser-printed 3D titanium porous implant ("Laser 3D," Group 1) and a titanium plasma-sprayed porous implant ("TPS," Group 2). Each implant was fabricated as a cylinder (6 mm diameter, 25 mm length) and implanted bicortically in the sheep tibia. Euthanasia and osseointegration assessment were conducted at 4 and 12 weeks. With three bicortical dowels per tibia and four animals, a total of 12 cortical implantation sites were assessed per time point per implant group. Assessments included a mechanical push-out test (measuring shear strength) and histomorphometric image analysis (quantifying bone ingrowth). For the bone ingrowth analysis, besides the traditional BIAV metric (with a unit of %), an alternative method was used. In this method, the absolute bone ingrowth volume (area in the 2D analysis) at the porous implant interface was measured and normalized by the implant length in the image. This metric, referred to as "bone per unit implant length" (BPUIL), has a unit of mm²/mm (or mm) and characterizes the absolute amount of bone integrated into the implant's porous structure. The two implant groups were compared in terms of osseointegration using both BIAV and BPUIL, and results were compared with shear strength measurements.

RESULTS: Histology and histomorphometry data showed that both implants achieved substantial bone ingrowth by 4 weeks post-surgery, with further increases at 12 weeks in concert with bone remodeling (Fig. 1). Mechanical push-out tests revealed significantly higher shear strengths at the cortical bone-implant interface from 4 to 12 weeks for both implant types (Fig. 2), with Laser 3D showing higher shear strength than TPS ($p < 0.05$ at 4 weeks). When quantifying the bone ingrowth on histomorphometric images, the BIAV method reflected increased osseointegration from 4 to 12 weeks but could not differentiate between implant types (Fig. 3, left). In contrast, the BPUIL method differentiated implant performance, showing greater bone ingrowth in Laser 3D implants ($p < 0.05$), which aligned with their higher shear strength in the push-out test (Fig. 3, right).

DISCUSSION: Preclinical animal studies are often used to assess the *in vivo* performance of porous metallic implants, including biocompatibility, tissue reaction, mechanical behavior, and, most importantly, osseointegration. To characterize osseointegration with histomorphometric images at the bone-implant interface, various methods can be employed. In the literature, BIAV is a commonly used metric for this purpose; however, because BIAV uses the available void as the denominator, if one implant has significantly lower porosity (i.e., less void) than another, BIAV may artificially favor the implant with less void, leading to biased comparisons. In this study, for example, the TPS implants had a less porous structure compared to the Laser 3D implants (porosity ~35% vs. ~65%), and BIAV measurements showed nearly identical values for the two implants, which couldn't explain the differences in push-out shear strength. In contrast, BPUIL quantifies the absolute volume of bone tissue integrated into the porous implant (normalized by implant length) and showed a clear advantage for the Laser 3D implants, better correlating with shear strength comparisons between the two implants. When comparing osseointegration between metallic implants with differing porosities, BPUIL tends to provide more meaningful results than BIAV.

SIGNIFICANCE/CLINICAL RELEVANCE: Porous metallic implants are increasingly used in orthopedics for biological fixation, providing secure, long-term stability without the need for cement. When studying the *in vivo* osseointegration performance of these implants, different measurement methods each have distinct advantages and limitations. Therefore, study designers should carefully select the most appropriate quantification methods to accurately capture the relevant characteristics of the implant devices.

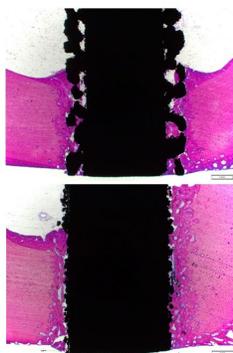


Fig 1. Cortical ingrowth at 12 weeks (top: Laser 3D, bottom: TPS)

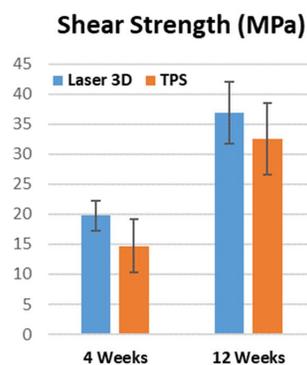


Fig 2. Shear strength results measured from push-out test.

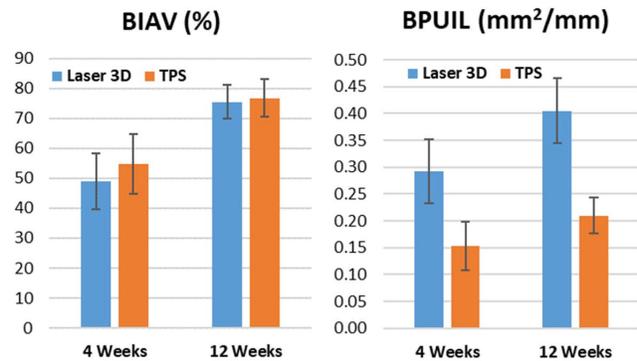


Fig 3. Bone ingrowth calculation using BIAV and BPUIL methods. BPUIL was able to capture the osteointegration differences between the two implants consistent with shear strength testing, while BIAV couldn't.

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