Bioactive Glass and Vitoss Bone Graft Substitute

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Introduction

Larry Hench, of the University of Florida, is credited with discovering bioactive glass in the late 1960s. Bioactive glass is a surface reactive glass-ceramic biomaterial originated from a research proposal funded by the US Army Medical Research and Development Command. The hypothesis of this initial research was [1]:

"The human body rejects metallic and synthetic polymeric materials by forming scar tissue because living tissues are not composed of such materials. Bone contains a hydrated calcium phosphate component, hydroxyapatite [HA] and therefore if a material is able to form a HA layer in vivo it may not be rejected by the body"

This research resulted in a 1971 article describing the in vivo interaction of bioactive glass with bone [2]. Since this initial publication, four decades worth of research have produced over 1000 articles on the topic of bioactive glass. Many of these articles describe the mechanisms by which bioactive glass can stimulate bone formation. Recent research on the specific formulation of bioactive glass used in the bioactive forms of the Vitoss Bone Graft Substitute has demonstrated its ability to stimulate cellular activity in vitro and improve healing in vivo [3,4].

Combeite 45S5 Bioactive Glass

Stryker's proprietary bioactive glass, Combeite 45S5, is comprised of 45 mol% SiO2, 25 mol% CaO, 25 mol% Na2O and 5 mol% P2O5 [5]. Upon implantation, 45S5 bioactive glass releases soluble ionic species include Si+, Ca2+, and Na+ into the surrounding environment [6].

This ionic dissolution initiates a series of reactions leading to the deposition of a hydroxycarbonate apatite layer on the surface of the bioactive glass which facilitates bone forming osteoblast cell attachment to the surface [6]. Additionally, these ions have been shown to elicit a cellular response including increased cell proliferation and enhancement of the osteogenic phenotype [7-9].

In Vitro Testing of Combeite 45S5

Testing was performed to investigate the in vitro response of human mesenchymal stem cells (hMSC) and primary osteoblasts to the presence of dissolution products of Combeite 45S5 bioactive glass (particle size mix of 32-90 μm and 90-150 μm). Cells exposed to dissolution products were compared to cells cultured in a control medium without bioactive glass dissolution products. When compared to cells cultured under control conditions, hMSC and primary osteoblasts cultured in glass-eluted medium demonstrated increased cellular proliferation **(Figure 1)**, increased collagen elaboration, and increased mineralization **(Figure 2)**[3].The increased mineralization and collagen elaboration seen in the hMSC group is particularly notable as it indicates a potential for the bioactive glass dissolution products to influence cells towards osteogenic differentiation in the absence of traditional differentiation reagents or exogenous growth factors. Additionally, culture in the presence of bioactive glass dissolution products further enhanced the native osteogenic phenotype of primary osteoblasts. This was demonstrated by greater deposition of collagen and mineralized matrix relative to untreated controls.

Figure 1

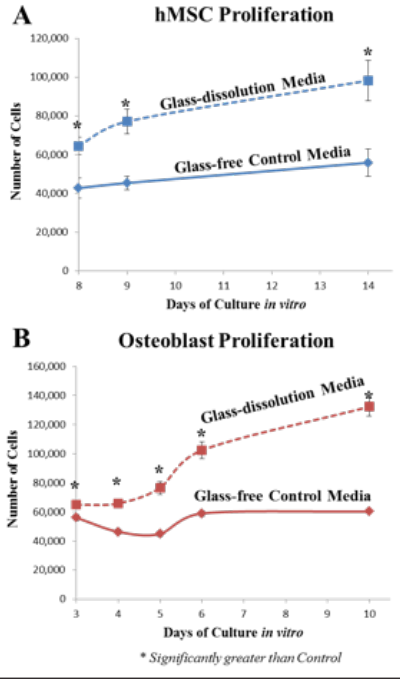

Figure 1. Proliferation of hMSC (A) and osteoblasts (B) significantly increased in response to culture in bioactive glass-dissolution media. (n=4, p<0.05) [3]

Figure 2

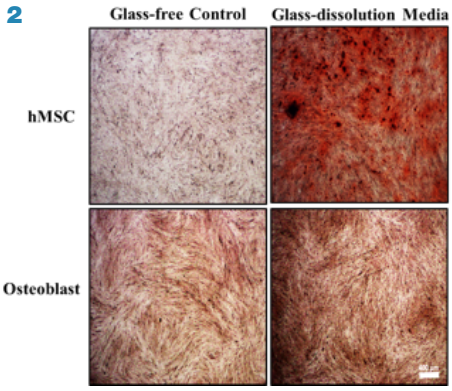

Figure 2. Alizarin Red mineralization staining of calcium deposition by hMSC (Day 28) and osteoblasts (Day 14) demonstrates increased mineralization in the presence of glass dissolution medium compared to glass-free controls. [3]

In Vivo Testing of Combeite 45S5

Bioactive forms of Vitoss combine Combeite 45S5 bioactive glass (90-150 µm particle size) with a composite of highly porous beta-tricalcium phosphate (β-TCP) and bovine Type I collagen. A canine model using a critical sized defect in the proximo-lateral humeri was used to compare a bioactive form of Vitoss to a form consisting only of the β-TCP and collagen [4]. While both groups demonstrated successful bony in-growth and resorption of the implant over the 52-week study period, mechanical testing of the defect site revealed a 6-12 week faster return to native strength for the bioactive group when compared to the control (**Figure 3A**). The Vitoss Bioactive group was 30% stronger than the control at 12 weeks (although not statistically significant) and 23% stronger at 24 weeks (statistically significant; $p<0.05$). Histological analyses showed that the faster restoration of strength may have been the result of increased interconnectivity of new bone growing within the Vitoss Bioactive group, demonstrated by bridging of new bone between β-TCP scaffold morsels (**Figure 3 B, C),** ultimately resulting in a stronger trabecular network throughout the defect site.

Figure 3

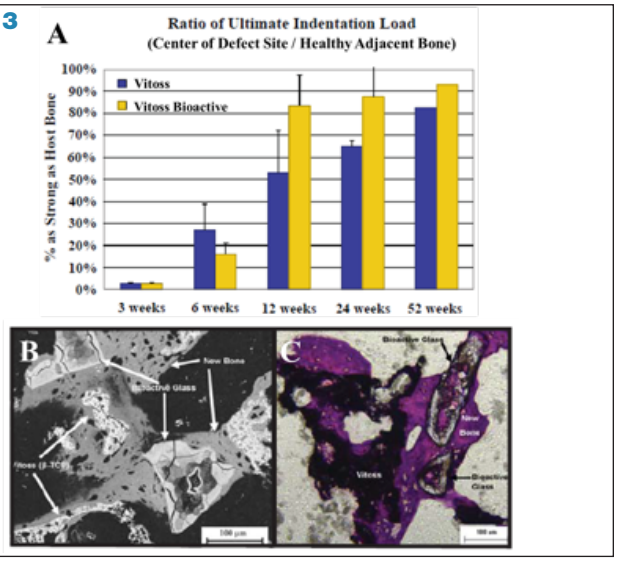

Figure 3. Mechanical indentation testing of canine implants demonstrated an increase in strength over time for both groups with the strength at the center of the defect approaching that of healthy adjacent bone (A). Backscatter electron image of an unstained Vitoss Bioactive sample at 6 weeks post-surgery illustrates that new bone developed on and around the β-TCP and bioactive glass (B). H&E staining indicated new bone (stained purple) formed, not only on and around the surface of the bioactive glass, but also from the center of the glass granule outward (C). [4]

Conclusion

The ability of bioactive glass to impact bone regeneration has been extensively studied over the last four decades, and well-established data demonstrates the chemical properties of glass facilitate a cellular response [6-9]. Research on Stryker's proprietary formulation of bioactive glass used in bioactive forms of Vitoss Bone Graft Substitute supports the literature and demonstrates and compared to glass-free controls, the presence of bioactive glass:

- Increases cellular proliferation in vitro.
- Enhances the osteogenic phenotype in vitro.
- Increases the rate of bone growth in a animal model.

Further research is needed to confirm how these findings may translate to clinical applications of Vitoss containing bioactive glass.

References
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