BoneSync™ BioActive Matrix Scientific Update

BoneSync BioActive is a second-generation synthetic bone void matrix that features a sophisticated trio of components, including bioglass 45S5. BoneSync BioActive matrix is osteoconductive and osteostimulative, allowing for bony ingrowth across a graft site. This elicits resorption and replacement by new bone during the body's native healing process. 45S5 bioactive glass provides a favorable environment for regeneration and cell attachment,[1] the release and exchange of ions to promote rapid bone formation,[2] and the ability to stimulate cell growth and support differentiation of osteoblasts.[3]

Basic Science of Bioactive Glass

Hench LL

The story of Bioglass. *J Mater Sci Mater Med*. 2006;17(11):967-978. doi:10.1007/s10856-006-0432-z

- A history of bioactive glasses, including the discovery and creation of bioglass, its characterization, in vivo and in vitro evaluation, clinical studies, and product development.
- When bioglass was discovered in 1969, in vitro testing in rats showed hydroxyapatite (HA) crystals bonded to layers of collagen fibrils produced by osteoblasts at the interface between bioglass 45S5 and native bone.
- Quantitative evaluations in rat and monkey models showed that the strength at the interface between bioglass and cortical bone was equal to or greater than the strength of host bone.
- Bioglass releases controlled rates of ionic dissolution products, such as soluble silica and calcium ions, that genetically drive proliferation and differentiation of osteoblasts.

Takeaway

Bioglass has an extensive history and is a class A bioactive material that induces osteoconduction and osteoproduction through the controlled release of ions, creating a strong interface with native bone and driving the cell cycle of osteoblasts.

BONESYNC BIOACTIVE

Arthrex®

Gerhardt LC, Boccaccini AR

Bioactive glass and glass-ceramic scaffolds for bone tissue engineering. *Materials (Basel).* 2010;3(7):3867-3910. doi:10.3390/ma3073867

- Discusses 6 key factors that define a successful scaffold for bone-tissue engineering, including structural properties, materials, bioactivation, signaling molecules, biological requirements, and cells. Report emphasizes biomimicry of human bone—the tissue fabrication technique focusing on scaffold surface architecture— as the future of bone-tissue scaffolding.
- Pore size larger than 300 µm and a porosity greater than 90% are key components required for enhanced new bone formation.
- Discusses the mechanical properties of bioglass 45S5 compared to trabecular and cortical bone. Additionally, bioglass 45S5 has comparable values to cortical bone, except for a low fracture toughness.
- The bone-tissue scaffold that best mimics the mechanical properties and topographical characteristics of real bone has a polymer matrix with incorporated nanophase bioactive glass particles, according to research by Misra et al. This design produced high protein absorption, cellular interactions, and mechanical properties.

Takeaway

Bone-tissue engineering continues to develop towards scaffolds that best mimic human bone (bio-mimicry). However, the balance of maintaining mechanical strength and controlled ion dissolution while creating extremely porous structures with complex topography has yet to be fully achieved. Bioglass 45S5 best meets this challenge in vivo and remains the standard for other bioactive scaffolds with bone growth applications.

Schepers EJ, Ducheyne P

Bioactive glass particles of narrow size range for the treatment of oral bone defects: a 1-24 month experiment with several materials and particle sizes and size ranges. *J Oral Rehabil.* 1997;24(3):171-181.

- Canine study evaluating bone growth around bioactive glass particles in comparison to HA particles in vivo. After 1, 2, 3, 6, 12, and 24 months, the samples were harvested and histologically analyzed.
- While HA particles were difficult to pack into the bony defect, the bioglass particles formed a cohesive mass when in contact with blood. In addition, the 3-month samples of HA only resulted in new bone formation on the bony defect; there was no new bone present within the HA particles.
- 3-month samples of bioglass particles resulted in protective pouches of new bone growth independent of the bony defect. These pouches function as nuclei for further bone growth and repair enhancement.
- Bioactive glass with composition A (ie, bioglass 45S5) and a narrow particle size range (300 µm to 355 µm) showed superior bone repair response.

Takeaway

Small particle sizes of bioactive glass perform better than any particle size of HA by inducing rapid bone proliferation. Bioactive glass induces osteoprogenitor differentiation throughout and surrounding the defect to produce consistent bone repair, whereas HA induced bone growth is only seen at the initial defect location.

Bioactive Glass Mechanism of Action

Hench LL, Splinter RJ, Allen WC, Greenlee TK

Bonding mechanisms at the interface of ceramic prosthetic materials. *J Biomed Mater Res A*. 1971;2(1): 117-141. doi:10.1002/jbm.820050611

- Theoretical model explains the interfacial bonding between bone and glass-ceramic materials (variations of bioglass) based on in vitro and in vivo studies.
- Bioglass composition is based off of a SiO_2-P_2O_5-CaO-Na_2O system in which sodium ions serve as an effective flux during the synthesis of bioglass and as an aid in maintaining a physiological balance of sodium at the glass-ceramic interface while modifying the local pH. Silicon dioxide maintains the glass-like structure of the bioglass and decreases the solubility rate of other ions to provide stability to the material.
- A series of in vitro HA studies showed a noticeable crystalline phase at the interface between the bioglass and HA, increasing the strength of the bond between the two materials.
- In vivo studies showed the presence of partially ossified osteoid and collagen fibrils along the interface of bone and bioglass, indicating ossification.

Takeaway

Bioglass displays strong bonding properties with bone and provides a beneficial surface for new bone formation and cellular attachment.

Xynos ID, Hukkanen MV, Batten JJ, Buttery LD, Hench LL, Polak JM

Bioglass 45S5 stimulates osteoblast turnover and enhances bone formation In vitro: implications and applications for bone tissue engineering. *Calcif Tissue Int.* 2000;67(4):321-329. doi:10.1007/s002230001134

- Analyzed the ability of bioactive glass ceramics to induce osteogenic differentiation in human primary osteoblast cultures and investigated the mechanisms related to osteogenesis in an in vivo site.
- Bioactive glass ceramic and bioinert substrates were seeded with human primary osteoblasts and evaluated at 2-, 6-, and 12-day timepoints.
- The presence of 3-dimensional cellular structures was seen throughout the surface of bioglass 45S5 at day 6 onward, suggesting evidence of cell activation and thus more cells per unit area.
- Researchers noted an increase in apoptosis during the initial days in culture, suggesting an ability to induce remodeling within an osteoblast population. They confirmed this osteostimulative ability of bioglass through an analysis of osteoblast differentiation markers.

Takeaway

Bioglass displayed evidence of cell activation through in vivo testing and analysis of osteoblast differentiation markers.

Xynos ID, Edgar AJ, Buttery LD, Hench LL, Polak JM

Gene-expression profiling of human osteoblasts following treatment with the ionic products of Bioglass 45S5 dissolution. *J Biomed Mater Res*. 2001;55(2):151-157. doi:10.1002/1097-4636(200105)55:2<151::aid-jbm1001>3.0.co;2-d

- In vivo test of whether bioglass 45S5 stimulates bone synthesis through its direct contact with host cells after implantation or through ions released by the substrate during material absorption.
- Ribonucleic acid (RNA) extracted from both groups were analyzed via differential microarray analysis. Of the 1760 genes surveyed, 190 were expressed in osteoblasts at levels above background.
- Analysis of the composition of the bioactive glass median showed the silicon concentration increased 86-fold in comparison to the control medium. Calcium and phosphate levels also increased notably in the experimental median.
- Ions released into the experimental medium from bioactive glass are responsible for the rapid osteogenesis of the osteoblast culture. Both calcium and phosphate have been experimentally proven to stimulate bone mineralization through their specific cellular receptor responses, and Si has been proven to be an important component in regulating bone metabolism.

Takeaway

The ionic products of bioactive glass are responsible for changes in gene transcription of human osteoblasts. Specifically, the gene production induced by the bioactive glass ions are each linked to osteoblast proliferation. Further research must be done to link the production of calcium, phosphate, and silicon to the gene transcription changes they are responsible for.

Xynos ID, Edgar AJ, Buttery LD, Hench LL, Polak JM

Ionic products of bioactive glass dissolution increase proliferation of human osteoblasts and induce insulin-like growth factor II mRNA expression and protein synthesis. *Biochem Biophys Res Commun.* 2000;276(2):461-465.

- Tested insulin-like growth factor II (IGF-II) levels of osteoblasts in media with bioglass 45S5 and in control media to determine its relative indication of bioactive glass activity.
- Human osteoblasts isolated from the trabecular bone during total hip arthroplasties were treated with bioactive glass DMEM or control DMEM for 4 days. Total RNA was extracted and analyzed via differential microarray analysis. Polymerase chain reaction (PCR) testing to validate the microarray data was also completed.
- Silicon concentration in the experimental medium was 88x that of the control. Silicon is mitogenic for bone cells.
- Osteoblast cells in the experimental group increased by 155% compared to control.
- IGF-II expression level increased by 390% in the experimental group in comparison to control. There was a positive correlation between PCR analysis of IGF-II levels and microarray analysis, indicating result confidence.

Takeaway

This study suggests that the ionic products of 45S5 bioglass can lead to osteoblast proliferations. Specifically, IGF-II induced differentiation and can mediate osteogenesis.

Carbonate Apatite

Kanayama K, Sriarj W, Shimokawa H, Ohya K, Doi Y, Shibutani T

Osteoclast and osteoblast activities on carbonate apatite plates in cell cultures. *J Biomater Appl.* 2011;26(4):435-449. doi:10.1177/0885328210374672

- Evaluated osteoclastic and osteoblastic activity through mRNA expression of various enzymes, proteins, and type I collagen related to bone resorption and formation in HA, beta-tricalcium phosphate (β-TCP), carbonate apatite (CA), and titanium (Ti).
- Bone marrow cells from tibias of 7-week-old mice were cocultured with osteoblasts isolated from newborn mice and type I collagen gel to generate osteoclast-like cells that were seeded on CA, HA, β-TCP, and Ti environments.
- CA displayed a higher number of osteoclast-like cells (OCLs), an up-regulation of osteoclast-related genes, increased mRNA expression of cathepsin K and cysteine protease in multinucleated cells, increased expression of V-ATPase, increased mRNA levels of osteoprotegerin, and greater expression of type I collagen mRNA.

Takeaway

There are numerous ceramics available for bone regeneration. CA was shown to support osteoclast and osteoblast activity significantly through increased m-RNA expression of various enzymes, proteins, and type I collagen, as well as a higher number of OCLs.

Matsuura A, Kubo T, Doi K, et al

Bone formation ability of carbonate apatite-collagen scaffolds with different carbonate contents. *Dent Mater J.* 2009;28(2):234-242. doi:10.4012/dmj.28.234

- Examined the effect of carbonate contents on in vivo bone formation using carbonate apatite (CO_3Ap) plus collagen in a sponge scaffold with different carbonate contents and HA. Carbonate content has been found to significantly impact apatite crystallinity and solubility during the bone metabolism process.
- The CO_3Ap scaffold with 4.8 wt% appeared to have a crystallinity similar to that of human bone and higher bone formation ability. It is thought to create suitable metabolic conditions for bone in relation to crystallinity, which affects solubility.

Takeaway

Carbonate is a trace element essential to the human body and biological apatites and has previously been reported to be closely related to human metabolism. The studied scaffold created suitable metabolic conditions and had a higher bone formation ability compared to other carbonate wt%.

Comparative Literature

Oonishi H, Kushitani S, Yasukawa E, et al

Particulate bioglass compared with hydroxyapatite as a bone graft substitute. *Clin Orthop Relat Res.* 1997;(334):316-325.

- Animal study looked at bone proliferation rates in bioactive glass particulates versus synthetic HA.
- 6 mm defects were created in femoral condyles of rabbits and were filled with either bioactive glass or HA. Results were captured at 1, 2, 3, 6, and 12 weeks.
- At 2 weeks, new bone had formed around nearly all of the bioglass particles in the defect and new bone formed bridges with HA by 3 weeks with varied distribution.

Takeaway

Bioglass led to a much more rapid proliferation of new bone than HA. Researchers hypothesized this may occur due to the activation of a cellular mechanism that induces the secretion of growth factors as a result of the release of soluble silicon, calcium, and phosphate from bioglass when exposed to body fluids.

Lindfors NC, Koski I, Heikkilä JT, Mattila K, Aho AJ

A prospective randomized 14-year follow-up study of bioactive glass and autogenous bone as bone graft substitutes in benign bone tumors. *J Biomed Mater Res B Appl Biomater.* 2010;94(1):157-164. doi:10.1002/jbm.b.31636

- Randomized 14-year study with a goal of analyzing the long-term results of implanted bioactive glass compared to implanted autograft bone after benign bone tumor surgery.
- Ten patients received bioactive glass S53P4 and 11 received autogenous bone. At the 14-year checkup, all 21 patients showed normal limb function and ROM at the graft implantation site.
- MRI scans, X-rays, and CT scans of each patient were completed for analysis. In the bioactive glass group, the patients' cavities were filled with dense, healthy bone.
- While glass granules among new bone were still visible, this is benign and due to the resistance of bioactive glass to osteoclastic activity. In addition, bioactive glass resulted in thicker cortical bone than normal, again with no adverse effects.

Takeaway

Bioactive glass S53P4 demonstrated good long-term results and is a safe and well-tolerated option for bone regeneration. The healing process from bioactive glass implants is comparable to that of autograft bone. There are no objections against bioactive glass synthetic bone grafts for use in adults.

References

1. Hench LL, Polak JM, Xynos ID, Buttery LD. Bioactive materials to control cell cycle. *Mat Res Innovat.* 2000;3(6):313-323. doi: 10.1007/s100190000055
2. Gerhardt LC, Boccaccini AR. Bioactive glass and glass-ceramic scaffolds for bone tissue engineering. *Materials (Basel).* 2010;3(7):3867-3910. doi:10.3390/ma3073867
3. Xynos ID, Hukkanen MV, Batten JJ, Buttery LD, Hench LL, Polak JM. Bioglass 45S5 stimulates osteoblast turnover and enhances bone formation In vitro: implications and applications for bone tissue engineering. *Calcif Tissue Int.* 2000;67(4):321-329. doi:10.1007/s002230001134