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Geometric Effects of Open Hollow Hydroxyapatite Microspheres Influence Bone Repair and Regeneration in Sprague Dawley Rats

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Statement of purpose: Effective regeneration of bone defects caused by trauma or chronic diseases is a significant clinical challenge. Bone deficiency is overcome using treatments that rely on bone regeneration and augmentation. While various treatments have been investigated with encouraging results, complete and predictable bone reconstruction is often difficult [1]. Synthetic bone grafts have advantages such as consistent quality, safety, and good tissue tolerance. They usually function as inert or osteoconductive implants. Encouraging results from synthetic grafts have been reported. For instance, hollow hydroxyapatite (HA) microspheres showed the ability to facilitate bone repair in rats with non-healing calvarial defects [2,3]. However, new bone formation with the closed HA microspheres was limited. Our goal is to investigate whether open HA microsphere mediated bone repair and regeneration in an osseous model is more effective than repair mediated by closed HA microspheres. The microgeometry-, size-, and time-dependent effects of bone repair by closed and open microspheres are also compared.

Methods: Closed hollow HA microspheres were converted from solid glass microspheres in an aqueous phosphate solution. The open HA microspheres were obtained by sectioning closed HA microspheres. Microspheres of two size ranges (ϕ106-150 μm and ϕ212-250 μm) were characterized using X-ray diffraction (XRD), Fourier-transform infrared (FTIR) spectroscopy, scanning electron microscopy (SEM), and the Brunauer-Emmett-Teller (BET) method. For *in vivo* studies, calvarial defects of male Sprague-Dawley rats were implanted with closed and/or open hollow HA microspheres for 6 weeks and 12 weeks. After 6 or 12 weeks, the animals were sacrificed by CO_2 inhalation, and the calvarial defect sites with surrounding bone and soft tissue were harvested for histological evaluations.

Results and discussion: The open HA microspheres had dense convex surfaces and rough, porous concave surfaces. For both size ranges (106-150 μm and 212-250 μm), the open HA microspheres were more effective in facilitating bone regeneration than the closed HA microspheres in calvarial defects of Sprague-Dawley rats. Bone regeneration with open HA microspheres (49 ± 7% for 106-150 μm; 40 ± 8% for 212-250 μm) was higher than that with closed HA microspheres (26 ± 8% for 106-150 μm; 30 ± 9% for 212-250 μm) at 12 weeks. Furthermore, the open HA microspheres of smaller size showed a significant increase in bone regeneration compared to the open larger sized microspheres at both 6 weeks and 12 weeks (p's< 0.05, N = 5-10).

Conclusions: Collectively, our study indicated that the open HA microspheres with certain microgeometry (i.e., concave, rough, and porous surfaces) could enhance bone regeneration significantly more than the closed HA microspheres. The capability of their osteogenesis was size- and time-dependent.

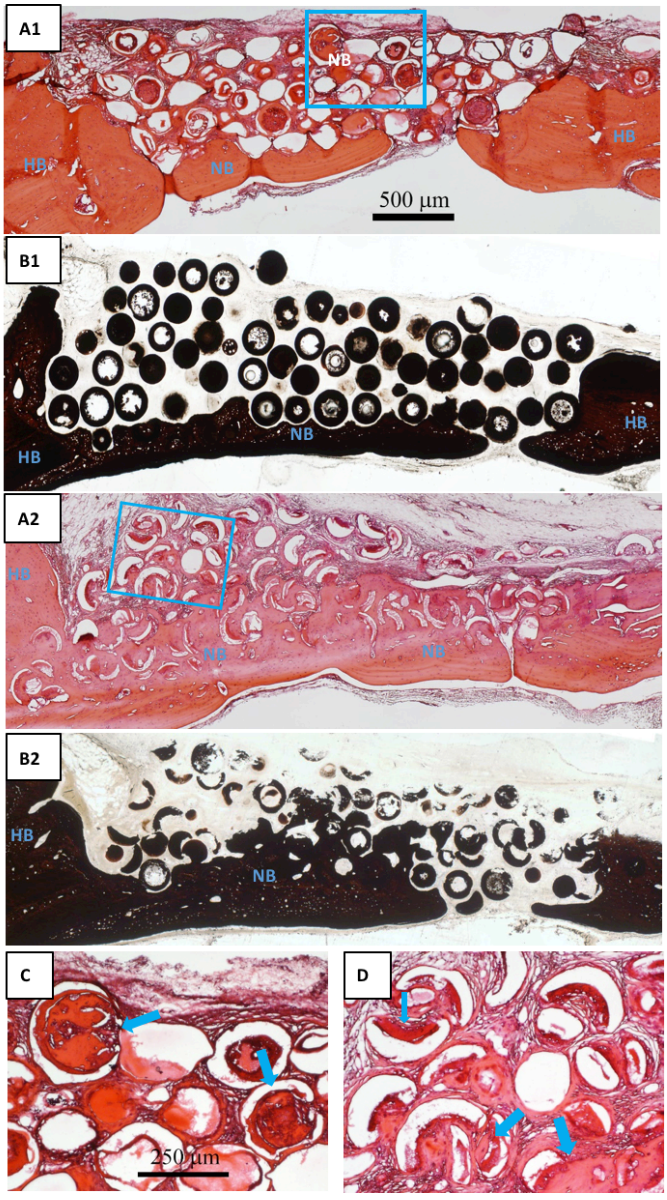

Figure 1. H&E and von Kossa stained sections of implants composed of closed (A1, B1) and open (A2, B2) HA microspheres (ϕ106-150 μm) after 12 weeks in rat calvarial defects; (C, D) higher-magnification images of boxed area in (A1, A2). HB: host bone; NB: new bone. Blue arrow: new bone growth in micro-concavity.

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