Orthogem TriPore HA:
A New Resorbable Hydroxyapatite (HA) Bone Graft Substitute –
Proof of Biological Concept in a Long-Term Sheep Femoral Condyle Model

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INTRODUCTION

Orthogem TriPore-HA, a resorbable synthetic bone graft (SBG), has been developed based on a new concept which defines a successful bone grafting procedure as restoring homogeneous osteocyte density of the implant area. Fast osteoingrowth did not warrant the SBG integration in the long term bone remodelling process, which was neglected by many SBG developers in the past thirty years.

The novel TriPore HA structure consists of macropores (>100μm), midipores (10~100μm) and microspaces (1~10μm). This structure allows early population of the graft with osteocytes not only inside the connecting macropores but also inside the ceramic body.

Development of a resorbable HA is of great interest to orthopaedic surgeons as the mechanical strength associated with HA products would be available, but ultimately the implant would be fully replaced by host bone, leaving no biological "hostages to fortune".

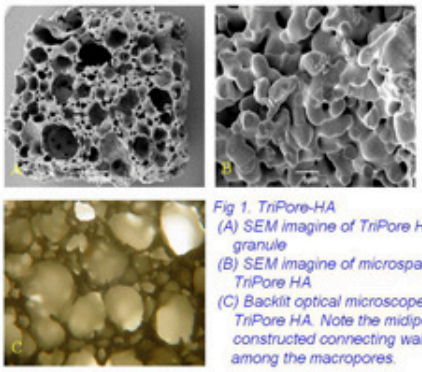

Fig 1. TriPore-HA
(A) SEM imagine of TriPore HA granule
(B) SEM imagine of microspace of TriPore HA
(C) Backlit optical microscope of TriPore HA. Note the midipore constructed connecting wall among the macropores.

This study quantitatively compares Orthogem TriPore HA to a commercially available ultraporous SBG, *Vitoss* from Orthovita Inc. (Malvern, PA).

MATERIALS AND METHODS

TriPore HA implants measured 7.9mm diameter x 15mm long. The control sample, Vitoss (β-TCP), measured 8mm x 15mm. The study was performed in accordance with the Home Office Animals Scientific Procedures Act.

Pairs of SBG blocks were implanted into each medial femoral condyle of skeletally mature sheep 0.5cm apart. Animals (n=18) were sacrificed at 6, 12 and 24 weeks post implantation.

The implants post retrieval underwent fixation in formalin, serial dehydration in alcohol and were embedded in resin for non-decalcified histology. The specimens were cut in line with the trabeculae of the distal condyle femur (Exact Saw). Thin sections (80-100μm) were then prepared and stained with Toluidine Blue and Paragon.

Analysis of bone and soft tissue formation within each implant (histomorphometry) was carried out using a point counting linear intercept technique and a computerised threshold sequencing method. Data was analysed using SPSS software and Paired Mann Whitney U tests were applied to the non-parametric data.

Half of a single TriPore HA before and after 24 week *in vivo* samples also analysed by micro-CT, μCT-40 from Scanco Medical Switzerland, with a resolution to 20μm. 900 cross scan was made for the whole implant. Under this resolution any midipores and microspaces smaller than 20μm will not be count as soft tissue or new bone but count as implant.

RESULTS

Tripore-HA implants showed rapid mature lamellar bone formation with extensive vascularization after 6 weeks *in vivo*. In macropores, the inside surfaces of the implants were covered with new bone in a lamellar pattern, organized circumferentially. The midipores, which form the connecting walls between the macropores, and the microspaces were completely filled with a combination of bone and osteocytes.

At six weeks bone appeared to be better organised in TriPore HA implant as evidenced by the presence of woven bone in Vitoss and the presence of lamella bone in TriPore HA. At 6, 12 and 24 weeks, all implants showed bone remodelling at the interface with new bone between the implant and the cortex.

Histology showed a significantly greater soft tissue component within the Vitoss implants compared to the TriPore HA samples (Table 1). This was consistent with signs of macrophage induced degradation of the Vitoss implants which was less apparent for the TriPore HA implants.

Implant Type	Bone formation %	Implant %	Soft tissue formation %
TriPore-HA			
T=0	-	51.1 ±2.8*	-
6 weeks:	25.5± 6.3**	44.6 ± 6.4*	30.0 ± 4.5*
12 weeks:	37.0±7.2	42.5±1.1*	20.5±6.7*
24 weeks:	32.2 ±7.0	39.9±4.5*	27.9±5.5*
Vitoss TCP			
T=0	-	38.3 ± 3.3	-
6 weeks:	28.8± 5.2	20.8 ± 7.5	50.5 ± 11.6
12 weeks:	40.9±5.2	11.1±1.7	48.1±5.9
24 weeks:	37.5 ±6.2	14.4 ±2.5	48.2 ±7.5

Table 1. Quantitative histomorphometry at 6, 12 and 24 weeks (mean ± standard deviation).
*Compared to Vitoss control, * p = <0.05, ** = p>0.05.*

The resolution of the micro-CT is much higher than the point counting technique used in the histology. As shown in the Table 2. Micro-CT showed 50% resorption of the TriPore HA implant after 6 months *in vivo* with equivalent bone substitution with 18.9% of the implant residual in the new bone matrix. The CT scan also indicated the TriPore HA implant was remodelled according to the surrounding cancellous bone structure, as shown in figure 2.

Sample ID number / Time / Analysis Technique	Implant Volume %	Bone Volume %
TriPore-HA ID 2784 / T=0 / Histology point counting	51.1 ±2.8	-
TriPore-HA ID 2784 / T=0 / Micro-CT	36.4	-
TriPore-HA ID 2784 / 24 wks / Histology point counting	38.9 ±6.7	28.7±5.44
TriPore-HA ID 2784 / 24 wks / Micro-CT	18.9	46.7

Table 2 . The difference between linear intercept counting of histology and micro-CT.

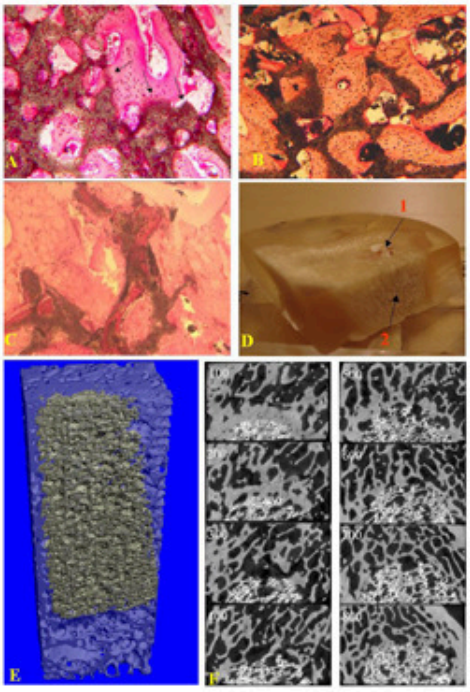

Fig 2.
(A) TriPore HA 6 weeks in vivo with intensive osteoingrowth and sign of HA degradation without macrophage reaction.
(B) TriPore HA 24 weeks in vivo the osteocytes colonized the ceramic structure and HA broke down for integration.
(C) Vitoss 6 weeks in vivo with excess soft tissue and woven bone formation
(D) The concave shrinkage of the Vitoss implant site after 24 weeks in vivo(arrow 1). The normal surrounding cancellous host bone.
(E) The micro-CT 3-D picture shows the remain TriPore HA in the implant site after 24 weeks.
(F) Each individual CT scan from number 100 to 800 with 100 interval, clear shown the TriPore HA was remodelling according to the surrounding bone structure.

CONCLUSION

This study shows that the unique porous structure of Orthogem TriPore-HA achieves rapid osteointegration whilst the implant resorption rate matches the rate of bone ingrowth, resulting in a robust and viable implant site. The results also demonstrate the structure efficiently re-establishes a homogenous osteocyte density not only in the macropores but also inside the ceramic implant body to ensure bone remodelling occurs throughout the whole of the implant.

Clinical trials of Orthogem Tripore–HA have now started in patients undergoing lumbar spinal fusion.