The Influence of Bisphosphonate Treatment on a Hydroxyapatite-Collagen Composite.

Sugata, Y; +1Sotome, S; 1Maehara, H; ... in the ALN group was not surrounded by newly formed bone (b). 

Bone HAp/Col

Fig.D(b) Fig.D(a) HAp/Col

Introduction: Bone substitutes, made mostly of calcium phosphates, have been developed recently with wide variation. Although sintered hydroxyapatite (HA), which is the most widely used bone substitute, is scarcely absorbed, other calcium phosphate materials, including hydroxyapatite / type I collagen composite (HAp/Col), developed by Kikuchi et al, are absorbed by osteoclasts and involved in natural bone remodeling mechanisms. Bisphosphonates have high affinity for HA and are adsorbed onto HA in bone tissues once injected or administered internally. Bisphosphonates adsorbed onto bone tissue induce apoptosis of osteoclasts and are thus widely used as drugs for the treatment of osteoporosis. They are also thought not only to alter natural bone remodeling mechanisms caused by osteoblast-osteoclast coupling but also to affect fracture healing. Many studies about the effects on fracture healing have been conducted, though the reported results remain controversial. Administered bisphosphonates are also adsorbed on to HA contained in transplanted bone substitutes and affect the healing process induced by artificial bone substitutes. There have been few reports about the effects of bisphosphonates on the healing process and the absorption of bioabsorbable bone substitutes, although there are some reports about their effects on allograft and autograft bone.

In this study, we transplanted porous HAp/Col, which has a sponge-like elasticity (Fig. A), into rabbit femur and evaluated the effects of alendronate on bone formation conducted by the implant and absorption of the implant.

Materials and Methods: A hydroxyapatite/type I collagen (HAp/Col) composite, aligning hydroxyapatite nano-crystals along collagen fibers, has been synthesized, and a porous body of the HAp/Col was prepared as a cylindrical implant, 6 mm in diameter and 8 mm in length, with a pore size of 100 to 500 µm and a porosity of 95 %. Eighteen Japanese white rabbits weighing 2.8 to 3.3 kg were used. Under general anesthesia, an implant was inserted into each right lateral condyle of the femur, where a cylindrical bone defect was created by drilling. Rabbits were divided into two treatment groups (9 rabbits per group): a saline control group and a systemic alendronate (ALN) administration group (7.5 µg/kg weekly, 0 – 6 weeks postoperatively). Rabbits were killed 3, 6, and 12 weeks postoperatively. Postmortem analyses included radiography, µCT and histology involving HE.

Results: HAp/Col implants of the ALN group exhibited reduced bone formation compared with the control group, even at 6 weeks postoperatively, when bone formation was shown to be most active. BMD of the implant area in the ALN treatment group was smaller than that in control group at 3, 6 and 12 weeks postoperatively (Fig. B-a). BMC indicated a similar tendency (Fig. B-b). Residual HAp/Col area per visual field was larger in the ALN group than in the control group throughout the experimental period, up to 12 weeks postoperatively (Fig. C). According to HE staining sections, new bone formation was seen on the surface of each HAp/Col, and most residual HAp/Col fractions were surrounded by the newly formed bone in the control group. In contrast, many large fractions of HAp/Col in the ALN group were exposed to the bone marrow directly at 12 weeks after surgery (Fig. D).

Discussion: We evaluated the effect of alendronate on bone formation conducted by porous HAp/Col. The amount of ALN administered in this study was established to be equivalent to that of the treatment of patients with osteoporosis, thus allowing an evaluation of the effects of clinical usage of bisphosphonate after implantation of bone substitutes. It might be expected that BMD and newly formed bone would be preserved in the ALN group because ALN inhibits bone resorption. However, our results show that bone formation was suppressed in the ALN group. The HAp/Col composite has similar biological properties to natural bone in both nanostructure and composition. It is resorbed by phagocytosis of osteoclast-like cells. Therefore, osteoconduction by HAp/Col partly would be due to osteoblast-osteoclast coupling, similarly to the natural bone remodeling mechanism. Thus, ALN inhibited the resorption of HAp/Col, resulting in the inhibition of the osteoconductivity of HAp/Col. Our study suggests that bone formation could increase if ALN begin to be administered after the peak of osteoconduction, and that ALN administration should be stopped temporarily after the implantation of HAp/Col or other bioreabsorbable bone substitutes in order to take advantage of its great osteoconductivity.


Fig. A. Porous HAp/Col composite. HAp/Col has a sponge-like elasticity and is good handling in surgical procedures.

Fig. B. (a, left): Bone mineral density, (b, right): Bone mineral content BMD and BMC of implant area in the ALN group was smaller than that in the control group through the period.

Fig. C. Residual HAp/Col area per visual field. Residual HAp/Col area per visual field was larger in the ALN group than in the control group throughout the experimental period, up to 12 weeks postoperatively.

Fig. D. HE staining of HAp/Col implanted in rabbit femoral condyle 12 weeks postoperatively. (a, left): control group, (b, right): ALN group. New bone formation is seen on the surface of HAp/Col in the control group (a). In contrast, a large fraction of HAp/Col in the ALN group was not surrounded by newly formed bone (b).