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Effect of strontium-containing hydroxyapatite bone cement on bone remodeling following hip replacement

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Abstract It is uncertain whether the use of bioactive bone cement has any beneficial effect on local bone adaptation following hip replacement. In this study, twelve goats underwent cemented hip hemiarthroplasty unilaterally, with either PMMA bone cement or strontium-containing hydroxyapatite (Sr-HA) bioactive bone cement. Nine months later, the femoral cortical bones at different levels were analyzed by microhardness testing and micro-CT scanning. Extensive bone remodeling was found at proximal and mid-levels in both PMMA and Sr-HA groups. However, with regard to the differences of bone mineral density, cortical bone area and bone hardness between implanted and non-implanted femur, less decreases were found in Sr-HA group than PMMA group at proximal and mid-levels, and significant differences were shown for bone area and hardness at proximal level. The results suggested that the use of Sr-HA cement might alleviate femoral bone remodeling after hip replacement.

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1 Introduction

Strontium (Sr) belongs to the same group as calcium (Ca) in the periodic table of elements, its beneficial effect at low dose in the treatment of osteoporosis was first reported over half a century ago [1]. However, considerable amount of attention on its therapeutic potential was paid only recently with the development of strontium ranelate. The current data indicate that strontium administration at low dose reduces bone resorption and increases bone formation [2–5], resulting with increased bone mass for normal and ovariectomized animals [6–8]. Clinical studies also showed that strontium administration to postmenopausal osteoporotic women resulted in a significant increase in bone mass and bone strength [9] by a dual mechanism of action: inhibition of bone resorption and augmentation of bone formation [10].

Due to its biological effect, researchers were interested on the development of bone cements containing strontium. Strontium has shown encouraging osteoconductivity of ionomeric cements when given at low doses [11]. Calcium phosphate ceramic materials, particularly hydroxyapatite (HA) and tricalcium phosphate (TCP) have been widely used in orthopaedics and dentistry because of their excellent biocompatibility with human hard tissues. On the basis of their chemical resemblances, partial Ca^{2+} in HA can be replaced by Sr^{2+}, which was noticed by the changes of materials dissolution behaviour and growth kinetics. Christoffersen et al. [12] investigated the dissolution behaviour of HA containing 1–10% Sr^{2+} in molar fraction instead of Ca^{2+} and found an increase of solubility for these apatites with increasing content of Sr^{2+}. Chen et al. [13] also proposed that the incorporation of strontium in low doses introduce more lattice distortions into the structure of HA and lead to the increase of its solubility. In

addition, the mechanical properties of this hydroxyapatite were found to be improved, when combined with 5% Sr in molar fraction of Sr/(Sr + Ca) instead of equivalent amount of calcium [14]. However, the investigation on the biological effect of Sr-containing bone cement on bone is still underway.

The understanding of biological effect of cement containing Sr on bone is of great clinical and theoretical interest. Bone cement can be applied in many clinical settings, such as joint replacement, vertebroplasty, screw augmentation and bone defect. Unfortunately, the quality of bone to which the conventional cement is bonded is usually inadequate. Therefore, Sr-containing bone cement would be an additional benefit in stimulating bone formation. Clinically, femoral bone loss following total hip replacement (THR) is a major concern because it can compromise the outcome of arthroplasty and may predispose to problems in revision arthroplasty surgery, if required [15]. Therefore, it should be of great advantage to undertake total hip replacement with bone cement containing Sr which can augment bone formation.

Strontium-containing hydroxyapatite (Sr-HA) bioactive bone cement is a bisphenol-A glycerolate dimethacrylate (Bis-GMA) based bone cement with 10% calcium ions in HA substituted by strontium. A series of studies have been conducted to show its biocompatibility, osteoconductivity and bioactivity [16–18]. Under both non-bearing and weight-bearing conditions, the dissolution of this bioactive bone cement was obtained, and Sr^{2+} was able to be traced at the interface of the bone [19, 20]. Extensive bone remodeling was demonstrated, especially at proximal femur, 9 months after cemented hip hemiarthroplasty with PMMA bone cement in our previous study [21]. Hence in this study, Sr-HA bioactive bone cement was further evaluated in a goat hip hemiarthroplasty model and compared with PMMA bone cement in regard with the differences of bone mineral density, cortical bone area, and bone hardness between implanted femur and non-implanted femur, thereby understanding if it has any beneficial effect on bone adaptation following hip replacement.

2 Materials and methods

2.1 Animal experiment

The institution's guide for the care and use of laboratory animals was followed. Both the goats rearing and the experiments were carried out according to guidelines for animal experiments at the University of Hong Kong. A total of 12 goats with a mean age of 9.6 years (age range, 7.0–13.0) were used. The mean weight of the goats was 37.5 kg (range, 35.0–43.0 kg). These animals were divided randomly into two groups. Unilateral cemented hip replacement model was created by the same experienced orthopaedic surgeon while six goats performed with Sr-HA bioactive bone cement and the other six with PMMA bone cement.

A pre-prepared ovine hemi-arthroplasty model was used in this study [21]. All surgeries were performed under general anaesthesia using aseptic techniques. Following a cranial incision over the junction of the tensor fascia lata and gluteobiceps, the deep gluteal tendon was exposed and transected. The underlying joint capsule was opened using a T incision, followed by transection of the ligamentum teres (round ligament) and the hip joint was dislocated. The femoral head was removed, medullary canal was reamed with rasps, and then the cavity was cleaned and dried. Subsequently, PMMA cement or Sr-HA cement was hand mixed and transferred into a syringe. The cement was injected into the medullary canal in a retrograde manner. The medullary canal was not plugged distally, and the bone cement was vacuum-mixed in this study. The custom-made hip prosthesis was inserted into the femur at a suitable position, and maintained until the cement was set. Finally, the joint was reduced, the range of movement was checked before the joint capsule was sutured, and the deep gluteal tendon was re-attached. The subcutaneous tissues and skin were closed and lastly the animal was recovered on a pan with a non-slip surface.

2.2 Sample preparation

All the goats were sacrificed nine months after injecting overdoses of pentobarbital intravenously, and their femurs were removed. Each implanted femur was transversely sectioned with a high-speed, water-cooled diamond saw (EXAKT 300 CP Band System, Norderstedt, Germany) into parallel sections of 10-mm thickness from the proximal end of the lesser trochanter. A total of six sections were obtained for each femur as shown in Fig. 1. In this study, section 2, 4, and 6 were used for testing, and regarded as the proximal level (PL), mid-level (ML) and distal level (DL), respectively. The contralateral non-implanted femurs were sectioned at the same anatomic locations for comparison. Push-out testing was performed on section 2 and 4 at the implanted side directly after the sectioning, during which the cement mantles were detached. Finally, the remaining bone blocks and section 6 at both sides, together with section 2 and 4 at the non-implanted side, were stored at −20°C for examinations.

2.3 Microhardness test

The surfaces of the section at proximal level were smoothed with polishing paper to increase fineness from

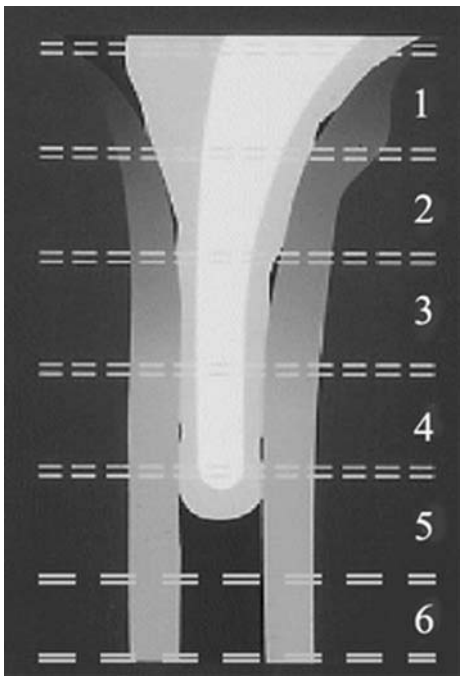

Fig. 1 Each femur was transversely sectioned into parallel sections of 10-mm thickness from the proximal end of the lesser trochanter, and a total of six sections were obtained

240 grit to 600 grit. The final polishing was carried out on a rotary wheel using 800 grit alumina abrasive in a moist medium. To minimize the effects of drying, the specimens were kept in a sealed container. Vickers microhardness test was performed by using a MHT-4 microhardness test machine fitted with a pyramidal diamond indenter (Zeiss, Germany). A mass of 50 g was used throughout the test. The pyramidal diamond indenter descent time was set at 10 s interval after which it was allowed to contact the specimen for 15 s. The dimensions of the indentation were measured 45 s after removal of the indenter. The diamond's diagonal pyramid of indentation was measured microscopically, and the following formula was used to calculate bone hardness:

$$H_V = 1854.4 \times L/d^2,$$

where H_V stands for Vickers Hardness and is expressed in kg/mm^2, L is the load in grams and d is the length of the indentation diagonal in mm.

Each bone section was divided into four sites; cranial, caudal, medial, lateral and each quadrant was based on its anatomic positioning. For each quadrant, five microhardess measurements were taken randomly from periosteal region to endosteal region. Therefore, the average value for each bone section was calculated from the sum of four sites.

2.4 Micro-CT

Following microhardness testing, all the samples were fixed in 4% neutral buffered formaldehyde (pH 7.2) for 3 days, and they were each dehydrated in alcohol solutions of 70, 80, 90, and 100% for 3 days, finally they were cleaned using xylene. The undecalcified samples were embedded in methylmethacrylate at 4°C. Subsequent to the solidification process, the femur were sectioned by intercepting perpendicularly to the long axis of the bone, 2 mm thick sections were made from the proximal end of the bone block using a cutting machine (EXAKT 300 CP Band System, Norderstedt, Germany).

Each section was scanned using a GE eXplore Locus SP Pre-Clinical Specimen MicroCT (GE Medical Systems) operated at a 50 μm isotropic voxel resolution. Hydroxyapatite (1.13 g/cm^3) was included in each scan and the specimens were immersed in water to provide control values for mineral content calculations. Bone tissue was segmented from non-bone tissue using the thresholding algorithm provided by the micro-CT manufacturer, and each sample was scanned continuously with thickness at an increment of 50 μm for 20 slices. The total cross-sectional images of the femoral sections were obtained. The cortical bone area (cm^2) and cortical bone mineral density (BMD, g/cm^3) of each section were measured.

2.5 Statistical analysis

The results were expressed as means ± standard deviation. Significant differences in BMD, cortical bone area, and bone hardness were determined by one-way analysis of variance (ANOVA). When statistical significant differences were found by the analysis of variance, Scheffe's test was employed (significance level: 5%) to test the hypothesis that there is a significant variation of BMD, cortical bone area, and bone hardness as functions of differences between implanted femur and non-implanted femur. As for the measured values between PMMA and Sr-HA groups, the paired *t*-test was chosen to determine whether they differ from each other in a significant way under the assumptions that the paired differences (implanted–non-implanted) are independent and identically normally distributed.

3 Results

After the operation, the goats were allowed unrestricted activity in their cages. Limited walking usually began within two or three days, and full activity was typical within two to three weeks. No infection was found during the study period. Six goats had a normal gait pattern one

Table 1 Microhardness, bone mineral density, and bone area at implanted and non-implanted sites by level in PMMA and Sr-HA groups

Group	Level	Microhardness (GPa)			Bone mineral density (mg/cm^3)			Bone area (cm^2)		
		Implanted	Non-implanted	*P* value	Implanted	Non-Implanted	*P*-value	Implanted	Non-Implanted	*P*-value
PMMA	PL	33.31 ± 7.42	42.13 ± 3.93	<0.001	531.67 ± 66.18	660.83 ± 65.10	0.004	1.11 ± 0.07	1.30 ± 0.06	<0.001
	ML	37.91 ± 5.66	42.29 ± 2.89	<0.001	531.17 ± 58.65	612.50 ± 49.19	0.010	1.18 ± 0.05	1.22 ± 0.04	0.015
	DL	42.15 ± 3.28	42.55 ± 3.56	0.308	565.50 ± 56.20	580.67 ± 28.84	0.339	1.16 ± 0.05	1.17 ± 0.04	0.667
Sr-HA	PL	36.82 ± 5.65	41.50 ± 5.90	<0.001	575.81 ± 64.89	653.69 ± 66.60	0.016	1.16 ± 0.04	1.29 ± 0.04	<0.001
	ML	40.78 ± 4.52	43.92 ± 4.51	<0.001	556.647 ± 36.84	622.75 ± 55.55	0.003	1.16 ± 0.03	1.21 ± 0.03	0.013
	DL	44.64 ± 4.36	45.23 ± 4.32	0.459	579.41 ± 22.43	591.26 ± 38.85	0.273	1.17 ± 0.04	1.18 ± 0.02	0.304

P-values are for comparisons between implanted site and non-implanted site

month after the operation. The others had a slight limp at the beginning, but resumed normal gait pattern three months post-operatively.

Nine months after cemented hip replacement, adaptive bone remodeling was identified in this study in both PMMA and Sr-HA groups, and their processes were characterized by a decrease in cortical bone area, bone mineral density, and microhardness. The results of cortical bone area, bone mineral density, and microhardness at different levels in both groups were shown in Table 1. In both PMMA and Sr-HA groups, there are significant differences ($P < 0.05$) in bone microhardness and BMD when implanted femurs were compared to the contralateral, nonimplanted femurs at PL (proximal level) and ML (middle level). However, no significant difference was found between implanted femurs and nonimplanted femurs at DL (distal level). On the other hand, compared with the non-implanted femur, the cortical bone area at the implanted femur with a significant decrease ($P < 0.05$) was found only at PL, not at ML and DL, for both PMMA and Sr-HA groups. In addition to the general bone remodeling for implanted femurs, a proximal-to-distal gradient change was also generated in this study with different performance for different variables in either PMMA or Sr-HA group (Fig. 2). Similar performance was found in bone microhardness, BMD, and bone area in these two groups.

Changes in each variable between implanted side and non-implanted side at different levels were compared between the two groups in regard with the differences of bone mineral density, cortical bone area, and bone hardness between implanted femur and non-implanted femur, and less decreases were found in Sr-HA group than PMMA group at proximal and mid-levels. Changes in bone hardness for Sr-HA group (GPa) at PL, ML, and DL were -4.68 ± 7.83, -3.13 ± 6.76, and -0.52 ± 6.05, respectively. For PMMA group, they were -8.82 ± 7.36, -4.39 ± 6.47, and -0.49 ± 3.88, respectively. This clearly shows there is significant difference ($P < 0.001$) only at PL between PMMA and Sr-HA group, but not at ML and DL (Fig. 3). Similarly, as for bone area, significant difference ($P < 0.05$) was found only at PL, but not at ML ($P = 0.189$) or DL ($P = 0.980$) between the two groups (Fig. 4). The bone area changes for Sr-HA group at PL, ML, and DL were -0.13 ± 0.02, -0.05 ± 0.03, and -0.02 ± 0.03, respectively. For PMMA group, they were -0.19 ± 0.05, -0.04 ± 0.03, and -0.01 ± 0.07, respectively. Lastly the changes in BMD (mg/cm^3), between two groups at PL (Fig. 5) have only shown marginal differences ($P = 0.066$). Changes in BMD for Sr-HA group at PL, ML, and DL were -77.87 ± 88.80, -66.29 ± 57.24, and -11.85 ± 33.83, respectively, and -129.16 ± 88.80; -81.33 ± 84.58, -15.16 ± 50.08, respectively for PMMA group.

4 Discussion

PMMA bone cement has been used for prosthetic fixation for almost 50 years. While clinically proven to be successful, there are still several problems associated with the use of this cement. The most serious one is that it does not adhere to bone, thereby allowing a fibrous layer to form between the bone surface and the cement [22], which is a major cause of the loosening of the cemented femoral components [23]. One suggested solution to overcome this problem at the interface is the use of bioactive bone cement [24]. Our previous studies [17] had demonstrated how Sr-HA bioactive bone cement has the potential to substitute the conventional PMMA bone cement, in which Sr-HA was used for hip replacement and was found to bond with bone directly. In our present study, this strontium-containing bioactive bone cement was further examined on its effect for hip replacement on femoral bone remodeling in a sheep model, and the results appear to show less serious femoral bone remodeling with the use of Sr-HA cement than PMMA bone cement, especially at the proximal level, suggesting that Sr-HA bioactive bone cement has positive effect to alleviate femoral bone remodeling.

Changes in architectural structure and bone mineral density of cortical bone after cemented THR were

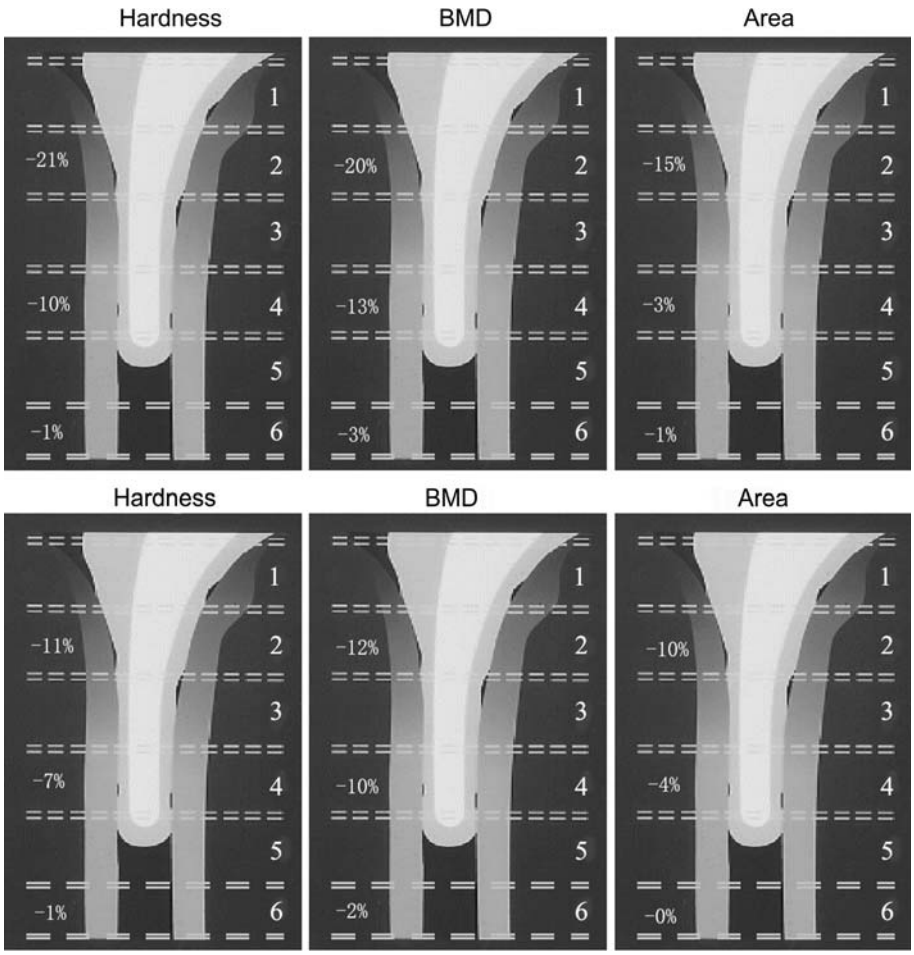

Fig. 2 Mean percentage change in bone microhardness, bone mineral density, and bone area comparing implanted with non-implanted site by level in PMMA group (UP) and Sr-HA group (DOWN)

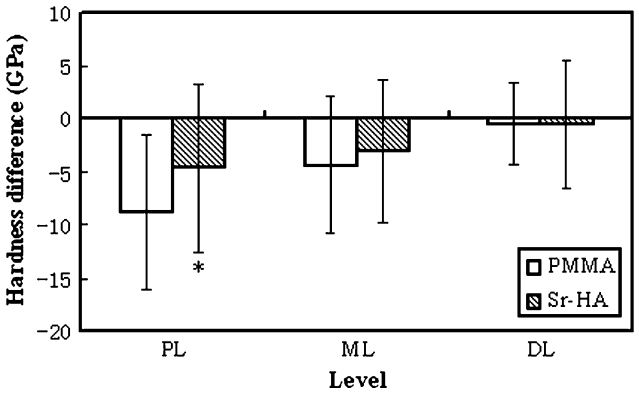

Fig. 3 Changes in bone hardness between implanted and nonimplanted sides at PL, ML, and DL in PMMA and Sr-HA groups. Significant difference was found only at PL ($P < 0.001$), not at ML ($P = 0.189$) and DL ($P = 0.980$)

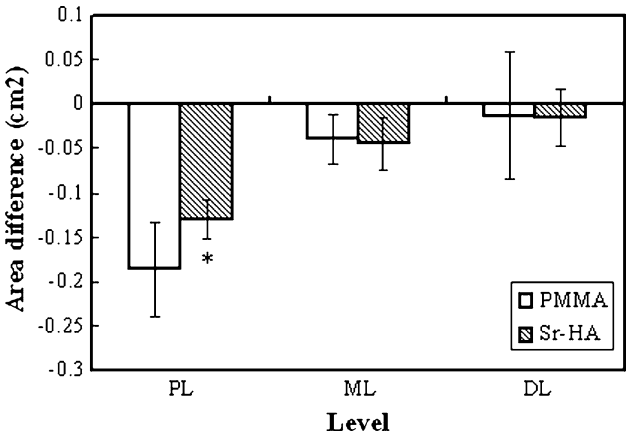

Fig. 4 Changes in cortical bone area between implanted and nonimplanted sides at PL, ML, and DL in PMMA and Sr-HA groups. Significant difference was found only at PL ($P = 0.049$), not at ML ($P = 0.707$) and DL ($P = 0.965$)

influenced by both mechanical and biological factors. Laboratory experiments have shown that insertion of cemented femoral components results in remarkable changes in the mechanical environment of the femur, especially at proximal level [25–27]. Femoral bone remodeling was previously examined by our research group following unilateral cemented hip hemiarthroplasty with PMMA bone cement, and the results suggested that stress-shielding is an important mechanical factor associated with bone adaptation [21]. This present study further demonstrated extensive bone remodeling at the proximal

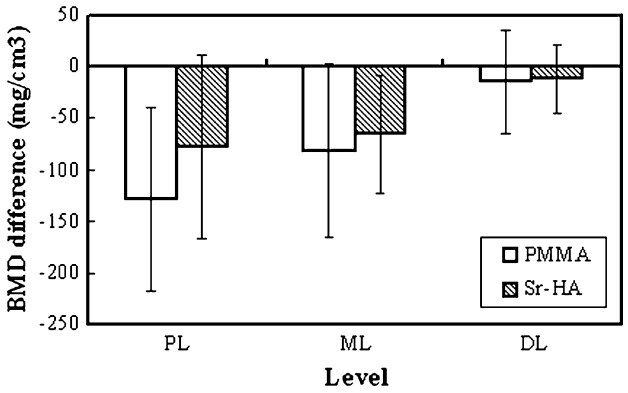

Fig. 5 Changes in bone mineral density between implanted and nonimplanted sides at PL, ML, and DL in PMMA and Sr-HA groups. No significant difference was found at PL ($P = 0.066$), ML ($P = 0.443$), or DL ($P = 0800$)

and mid-levels of the femur in PMMA group as well as Sr-HA group. Similar proximal-to-distal gradient trend of the femoral bone adaptation in both groups have clearly indicated that stress-shielding plays an important role in femoral bone remodeling following hip replacement with the use of either PMMA or Sr-HA bone cement.

For cemented arthroplasty, the femoral component is a composite with a stiff central core (the femoral stem) and a more flexible outer layer (the cement) that interdigitates with the surrounding bone to provide mechanical fixation. The force emitted from the mechanical load is transmitted from the implant through the cement to the bone and the significant change in the mechanical environment of the proximal femur is resulted from the insertion of cemented femoral components, regardless of the cement type used. Nevertheless, it is quite likely that the use of different types of cements may lead to different load alteration. When bone and implant (with different moduli of elasticity) are loaded next to each other, the stiffer implant bears the majority of the load. Such preferential load transfer through the implant seems to be proportional to the increasing stiffness of the material [28]. It is therefore thought that the load transmission is unlikely to be the same with different type of cements in between implant and bone. Another possible factor to affect the load transmission is the different in vivo bone-bonding behaviour between these two cements. Sr-HA bone cement can be bonded directly to the bone, whereas for PMMA cement, it is consisted of an intervening fibrous layer in-between the bone and the cement [22]. The exact effect of direct bonding between bone and cement on load alteration remains unclear, though, it was assumed that the direct bonding may be associated with greater stress-shielding and bone resorption [29]. To address this issue, both the mechanical properties of the bioactive bone cement and its bond-bonding behaviour should be taken into consideration in the future.

Although, mechanically the effect of bioactive bone cement on bone resorption following THR is still remains unclear, but from a biological point of view, bioactive bone cement is likely to have a positive effect. Wear debris is considered to be one of the major factors responsible for osteolysis. Several attempts at resolving this problem currently are in progress, one of which involves improving the characteristics of the bone cement interface [30–32]. The improvement of the characteristics at the bone–cement interface may be achieved by using bioactive bone cement, which has the ability to bond directly with the bone. Much higher affinity indices of Sr-HA bone cement have been shown than the PMMA bone cement at 6 months after implantation [17]. This may result in closer adhesion and less micromotion at the bone–cement interface of the Sr-HA group compared with the PMMA bone cement group, which means that cells that can phagocytize wear debris of polyethylene or metal or both, may not exist at the bone–cement interface.

A further advantage of Sr-HA bioactive bone cement is that the maximum temperature during polymerization was lower than that of PMMA bone cement [16]. Tissue damage around the cement mantle formed by this bioactive bone cement during hardening may be less than damage caused by PMMA bone cement [33]. More importantly, in contrast to PMMA cement, which was shown to inhibit bone formulation and induce bone resorption, cytotoxicity and inflammatory reactions [34], Sr-HA cement, a strontium-containing material, was supposed to stimulate bone formation. The effect of strontium in the form of strontium ranelate can inhibit bone resorption and augment bone formation, which has been well investigated in both in vitro and in vivo studies [2–10]. As to Sr-HA bone cement itself, Xue et al. [35] ever compared it with HA on cellular attachment, proliferation, and differentiation in vitro, and the results showed that the presence of Sr can stimulate osteoprecursor cell differentiation, and enhance alkaline phosphatase and osteopontin expression. Ni et al. [36] further reported that Sr-HA bioactive bone cement has the ability to induce new bone formation in vivo.

Although strontium is believed to stimulate bone formation locally, the release of strontium ion from the Sr-containing material should be a key step. A biomaterial's solubility may depend on the structure of material itself, as well as the type of bone it bonds with [19]. HA is classified as a surface-active bioactive material with low solubility. However, the substitution of Ca by Sr could cause a crystal lattice expansion due to the larger atomic radius of Sr, which in turn alters the solubility of the mineral [12]. As for the Sr-HA cement used, 10% calcium ion in HA was substituted by Sr, and its dissolution was previously demonstrated by high-resolution transmission electron microscopy (HR-TEM) after injected into rabbit ilium in an

animal model [28]. On the other hand, the Sr-HA cement bonds with cancellous bone at the proximal level and with cortical bone at the mid-level should be emphasized. Cancellous bone differs from cortical bone in many aspects, including vascularity and density [29, 30], which may result in different dissolution rate of Sr-HA bone cement when bonding with them. Considerably higher dissolution rate of Sr-HA cement was confirmed by EDX and ToF-SIMS in our previous study [19], when bonding with cancellous bone than with cortical bone. It is therefore suggested that more strontium ions were released from Sr-HA cement at PL than ML, thus leading to more bone formation at PL. This may explain the finding in this study that more prominent beneficial effect on bone remodeling at PL than ML of femoral bone.

5 Conclusion

Extensive bone remodeling was demonstrated at proximal and mid-levels in both PMMA and Sr-HA groups. However, with regard to the differences of bone mineral density, cortical bone area, and bone hardness between implanted femur and non-implanted femur, less decreases were found in Sr-HA group than PMMA group at proximal and mid-levels, and significant differences were shown for bone area and microhardness at proximal level, suggesting that comparing with PMMA cement, Sr-HA bioactive bone cement can alleviate femoral bone remodeling following hip replacement. Together with the previous studies demonstrating good in vivo bone bonding behaviour of this bioactive bone cement, the present study further signify the potential to substitute the conventional PMMA bone cement in the use of hip replacement.

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References

1. Shorr E, Carter AC. The usefulness of strontium as an adjuvant to calcium in the remineralization of the skeleton in man. Bull Hosp Jt Dis Orthop Inst. 1952;13:59–66.
2. Takahashi N, Sasaki T, Suda T, Tsouderos Y. S 12911-2 inhibits osteoclastic bone resorption in vitro. J Bone Miner Res. 2003;18:1082–7.
3. Baron R, Tsouderos Y. In vitro effects of S12911-2 on osteoclast function and bone marrow macrophage differentiation. Eur J Pharmacol. 2002;450:11–7.
4. Canalis E, Hott M, Deloffre P, Tsouderos Y, Marie PJ. The divalent strontium salt S12911 enhances bone cell replication and bone formation in vitro. Bone. 1996;18:517–23.
5. Barbara A, Delannoy P, Denis BG, Marie PJ. Normal matrix mineralization induced by strontium ranelate in MC3T3-E1 osteogenic cells. Metabolism. 2004;53:532–7.
6. Delannoy P, Bazot D, Marie PJ. Long-term treatment with strontium ranelate increases vertebral bone mass without deleterious effect in mice. Metabolism. 2002;51:906–11.
7. Modrowski D, Miravet L, Feuga M, Marie PJ. Increased proliferation of osteoblast precursor cells in estrogen-deficient rats. Am J Physiol. 1993;264(2 pt 1):E190–6.
8. Hott M, Deloffre P, Tsouderos Y, Marie PJ. S12911-2 reduces bone loss induced by short-term immobilization in rats. Bone. 2003;33:115–23.
9. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med. 2004;350:459–68.
10. Marie PJ. Strontium ranelate: a physiological approach for optimizing bone formation and resorption. Bone. 2006;38:S10–4.
11. Johal KK, Mendoza-Suarez G, Escalante-Garcia JI. In vivo response of strontium and zince-based ionomeric cement implants in bone. J Mater Sci: Mater Med. 2002;13:375–9.
12. Christoffersen J, Christoffersen MR, Kolthoff N. Effects of strontium ions on growth and dissolution of hydroxtapatite and on bone mineral detection. Bone. 1997;20:47–52.
13. Chen DM, Fu YF, Gu GZ. Preparation and solubility of the solid solution of strontium substituted hydroxyapatite. Chin J Biomed Eng. 2003;20:278–82.
14. Chen DM, Fu YF. Evaluation on the mechanic properties of the solid solution of strontium substituted hydroxyapatite. Chin J Stoma Mater Appar. 2001;19:178–83.
15. Duncan C, Masterson E, Masri B. Impaction allografting with cement for the management of femoral bone loss. Orthop Clin North Am. 1998;29:297–305.
16. Li YW, Leong JCY, Lu WW, Luk KDK, Cheung KMC, Chiu KY, et al. A novel injectable bioactive bone cement for spinal surgery: a development and preclinical study. J Biomed Mater Res. 2000;52:164–70.
17. Ni GX, Lu WW, Chiu KY, Li ZY, Fong DY, Luk KD. Strontium-containing hydroxyapatite (Sr-HA) bioactive cement for primary hip replacement: an in vivo study. J Biomed Mater Res. 2006;77B:409–15.
18. Wong CT, Lu WW, Chan WK, Cheung KMC, Luk KDK, Lu DS, et al. In vivo cancellous bone remodeling on a strontium-containing hydroxyapatite (Sr-HA) bioactive cement. J Biomed Mater Res. 2004;68A:513–21.
19. Ni GX, Lu WW, Xu B, Chiu KY, Yang C, Li ZY, et al. Interfacial behaviour of strontium-containing hydroxyapatite cement with cancellous and cortical bone. Biomaterials. 2006;27:5127–33.
20. Chen QZ, Wong CT, Lu WW, Cheung KMC, Leong JCY, Luk KDK. Strengthening mechanism of bone bonding to crystalline hydroxyapatite in vivo. Biomaterials. 2004;25:4243–54.
21. Ni GX, Lu WW, Chiu KY, Wang Y, Li ZY, Zhang YG, et al. Mechanical properties of femoral cortical bone following cemented hip replacement. J Orthop Res. 2007;25(11):1408–14.
22. Freeman MAR, Bradley GW, Revell PA. Observation upon the interface between bone and polymethylmethacrylate cement. J Bone J Surg. 1982;64B:489–93.
23. Jasty M, Maloney WJ, Bragdon CR, Haire T, Harris WH. Histomorphological studies of the long-term skeletal responses to well fixed cemented femoral component. J Bone J Surg. 1990;72A:1220–5.
24. Harper EJ. Bioactive bone cements. Proc Instn Mech Engrs. 1998;212:113–8.
25. Huiskes R. The various stress patterns of press-fit, ingrown, and cemented femoral stems. Clin Orthop. 1990;261:27–38.
26. Oh I, Harris WH. Proximal strain distribution in the loaded femur. J Bone Joint Surg. 1978;60A:75–85.
27. Silva MJ, Reed KL, Robertson DD, et al. Reduced bone stress as predicted by composite beam theory correlates with cortical bone

loss following total hip arthroplasty. J Orthop Res. 1999;17:525–31.
28. Bobyn JD, Glassman AH, Goto H, Krygier JJ, Miller JE, Brooks CE. The effect of stem stiffness on femoral bone resorption after canine porous-coated total hip arthroplasty. Clin Orthop. 1990;261:196–213.
29. Engh CA, Bobyn JD. The influence of stem size and extent of porous coating on femoral bone resorption after primary cementless hip arthroplasty. Clin Orthop. 1988;231:7–28.
30. Fujita H, Matsuda Y, Iida H, et al. Evaluation of bioactive bone cement in canine total hip arthroplasty. J Biomed Mater Res. 2000;49:273–88.
31. Labella R, Braden M, Deb S. Novel hydroxyapatite-based dental composites. Biomaterials. 1994;15:1197–200.
32. Saito M, Muraoka A, Mori T, Sugano N, Hino K. Experimental studies on a new bioactive bone cement: hydroxyapatite composite resin. Biomaterials. 1994;15:156–60.
33. Liu YK, Park JB, Njus GO, Stienstra D. Bone-particle-impregnated bone cement: an in vitro study. J Biomed Mater Res. 1987;21:247–61.
34. Lewis G. Properties of acrylic bone cement: state of the art review. J Biomed Mater Res. 1997;38:155–82.
35. Xue W, Moore JL, Hosick HL, Bose S, Bandyopadhyay A, Lu WW, et al. Osteoprecursor cell response to strontium-containing hydroxyapatite ceramics. J Biomed Mater Res. 2006;79A:804–12.
36. Ni GX, Chiu KY, Lu WW, Wang Y, Zhang YG, Hao LB, et al. Strontium-containing hydroxyapatite bioactive bone cement in revision hip arthroplasty. Biomaterials. 2006;27:4348–55.