ORIGINAL ARTICLE

Connective Tissue Reaction and Bone-cement Contact after Implantation of PMMA Resin Cements

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SYNOPSIS
Super Bond (SB) shows biocompatible and adhesive properties to bone as well as to dentin. In this study, SB induced minimal inflammation when implanted in connective tissue of rat, although Multibond II (MB) and Surgical Simplex® (SX) caused intense inflammatory response. SB was mostly in direct contact with bone without formation of fibrous tissue when implanted in the intramedullary canal of rat, although formation of fibrous tissue between resin cement and bone was mostly observed with MB and SX. Moreover, SEM observation revealed that SB was mostly in direct contact without a gap. Disorders of bone tissue or bone cells were not observed in the case of SB, MB and SX implanted in the intramedullary canal. Thus, 4-META/MMA-TBB cement can be effectively used as a bone cement.

Key words: 4-META/MMA-TBB resin, Bone cement, Biocompatibility, Bone, Adhesion

INTRODUCTION
Reconstruction of bone defects is a common challenge in the medical and dental fields. Autogenous bone has always been the gold standard for bone reconstruction, but its use implies an additional surgical procedure that may result in donor site morbidity; besides, its availability is naturally limited. Clinically, bone defects have been filled with a range of artificial materials, e.g., ceramics, polymers, and a combination of these.

Ceramics such as tricalcium phosphate (TCP) and hydroxyapatite (HA) are biocompatible and osteoconductive. These are available as porous or solid, blocks or granules. Thus, technical difficulties that arise when filling defects or shaping due to fragility and dispersion can be a disadvantage. Furthermore, ceramics require a long time to get resorbed and fixed to bone. β-TCP undergoes resorption via dissolution and fragmentation over a 6- to 18-month period. HA is resistant to resorption in
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vivo, which occurs at a rate of 1 to 2% per year\(^1\). Cement-type calcium phosphate materials, such as BIOPEX-R\(^5\) (Hoya Corporation, Tokyo, Japan), are self-setting cements used to fill bone defects. However, it takes more than 2 weeks for a thin layer of new bone to deposit onto the surface of BIOPEX-R\(^5\).

In contrast, polymers such as polymethyl methacrylate (PMMA) bone cement are self-setting and harden quickly. Thus, PMMA bone cement has been widely used to fix orthopedic prostheses for total hip arthroplasty\(^6,7\) or in an injection form for percutaneous vertebroplasty\(^8\). Total hip arthroplasty is one of the most successful and rewarding operations ever developed. In over 90% of cases, it provided good initial results, and most of these lasted for 7 to 10 years\(^9\). The quick-hardening property of PMMA bone cement allowed walking rehabilitation to be started between the 1st and 10th day postoperatively\(^10\).

However, the fixation of prostheses is attained through mechanical interlocking and not adhesion. If the formation of a fibrous layer between the bone surface and cement is observed, this can lead to loosening of the prostheses\(^11,12\). A number of papers have described series of cases in which loosening of the femoral component occurred. The reported incidence ranged from 1.1%\(^13\) to 36%\(^14\) or even 50% at 5.8 years\(^15\).

In endodontics, post-and-cores are frequently used for reconstruction of devitalized teeth. Nonadhesive cements, which rely on frictional forces, are used for the retention of posts. These nonadhesive cements are intended primarily to fill the space between the post and tooth tissue. This concept has to be revised with the introduction of adhesive resin cement, as adhesion contributes substantially to retention\(^16-18\). Clinical studies have shown that many post-and-core restorations fail over a period of years\(^19-21\). Cyclic loads during mastication can lead to fatigue of cement, resulting in disintegration of the cement. If leakage occurs at the same time, dissolution of the cement may further degrade the mechanical properties of the cement layer\(^22\), finally resulting in loosening of the post-and-core buildup. In this respect, adhesive resin cements may perform better over the long term than nonadhesive cements for post-and-core restorations. Thus, if an adhesive resin cement is used as bone cement, loosening of the prostheses due to formation of a fibrous layer can be prevented.

Adhesive resin cements are widely used in clinical dentistry because of their excellent adhesive properties to enamel, dentin, metal and ceramic\(^23\). Especially, 4-methacryloxyethyl trimellitate anhydride/methyl methacrylate tri-n-butylborane (4-META/MMA-TBB) resin (Super Bond, SB, Sunmedical Co. Ltd., Shiga, Japan) shows little cytotoxicity as it only interferes slightly with cultured cell attachment and proliferation\(^24,25\), and is less phlogogenous when implanted in connective tissue after complete curing\(^26\). Moreover, SB adheres to bone by the formation of hybridized bone\(^27\), and the adhesion shows long-term stability without interfering with bone remodeling\(^28\). If SB is used as bone cement to fix orthopedic prostheses for total hip arthroplasty, fixation of the prostheses may be attained through adhesion.

In this study, inflammatory reactions in connective tissue and direct contact to bone after implantation of SB and two other cements were histologically evaluated.

**MATERIALS AND METHODS**

**CEMENTS**

In addition to SB, Multibond II (MB, Tokuyama Dental Corporation, Tokyo, Japan) and Surgical Simplex\(^8\) (SX,
Stryker Japan K.K., Osaka, Japan) were used as controls. The components of each cement are listed in Table 1; the details were obtained directly from the cement packaging.

**ANIMAL EXPERIMENTS**

Experiments 1 and 2 were conducted in accordance with the institutional animal use and care regulations of Hokkaido University (Animal Research Committee of Hokkaido University, Approval No. 09-0089). All surgical procedures were conducted under anesthesia induced by diethyl ether and pentobarbital (Somnopentyl, Kyoritsu Seiyaku Corporation, Tokyo, Japan).

**EXPERIMENT 1**

Twenty 11-week-old male Wistar rats were used in this study. The back area of each rat was shaved. A 15-mm incision was made along both sides of the backbone, and a connective tissue pocket was created by blunt dissection of the subcutaneous lesion. A total of eight connective tissue pockets were formed on each rat. The connective tissue pockets were randomly assigned to the following five groups.

- **Group GA+SB**: The connective tissue pockets were treated with Green activator (GA, Sunmedical Co. Ltd., Shiga, Japan) for 5 s, washed with saline, dried, and SB was implanted by the brush-dip technique.
- **Group SB**: The connective tissue pockets were washed with saline, dried, and SB was implanted by the brush-dip technique.
- **Group Pr+MB**: The connective tissue pockets were treated with Primer (Pr, Tokuyama Dental Corporation, Tokyo, Japan) for 20 s, dried, and MB was implanted by the brush-dip technique.
- **Group MB**: The connective tissue pockets were washed with saline, dried, and MB was implanted by the brush-dip technique.
- **Group SX**: The connective tissue pockets were washed with saline, dried, and SX was implanted.

The incisions were then closed with sutures.

All animals were euthanized with an overdose of diethyl ether. Specimens were obtained at 1 and 2 weeks post-operatively. The specimens including the cements with the surrounding tissues were excised, fixed in 10% formalin and embedded in paraffin. Sections (5 μm thick) were prepared and stained with hematoxylin and eosin (H&E). Subsequently, histologic observations and histomorphometric analysis were performed under a light microscope.

**Table 1** List of the components of each cement

<table>
<thead>
<tr>
<th>polymer</th>
<th>PMMA</th>
<th>PMMA</th>
<th>PMMA</th>
<th>BPO</th>
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<tr>
<td>monomer</td>
<td>MMA</td>
<td>MMA</td>
<td>MMA</td>
<td>DMPT</td>
</tr>
<tr>
<td>1 META</td>
<td>UDMA</td>
<td>HEMA</td>
<td>hydroquinone</td>
<td>borate catalyst</td>
</tr>
<tr>
<td>conditioner</td>
<td>10% citric acid</td>
<td>3% ferric chloride</td>
<td>acetone</td>
<td></td>
</tr>
<tr>
<td>primer</td>
<td>phosphoric acid monomer</td>
<td>UDMA</td>
<td></td>
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</table>
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One H&E-stained section was taken from the center of the resin cement. The following two measurements were performed using image-processing software (Image J, National Institutes of Health, Maryland, USA).

S: The area of connective tissue in which more than 20 inflammatory cells were observed in 0.01 mm².
L: The major axis length of the resin cement.

The means and standard deviations of the extent of inflammatory cell infiltration (S/L) [μm] were calculated for each group. Differences among the groups were analyzed using the Tukey’s test; p-values < 0.05 were considered statistically significant. All statistical procedures were performed using a software package (Dr. SPSS II, IBM, Tokyo, Japan).

EXPERIMENT 2
Forty-six 11-week-old male Wistar rats were used in this study. A longitudinal incision was made over the anterolateral aspect of femora on both sides. The vastus lateralis and biceps femoris muscles were separated to expose the shafts of the femora. All attached muscles and periosteum were stripped from the shafts. A cortical bone perforation measuring 2×3 mm was created on the lateral aspect of the femur using a saline-cooled round bur, the bone marrow was curetted and the intramedullary canal was irrigated with saline, bleeding was arrested by pressure hemostasis with pledgets. The intramedullary canals were randomly assigned to the following three groups.

Group GA+SB: The intramedullary canals were treated with GA for 5 s, washed with saline, dried, and SB was implanted.
Group Pr+MB: The intramedullary canals were treated with Pr for 20 s, dried, and MB was implanted.
Group SX: The intramedullary canals were dried, and SX was implanted.

The incisions were then closed with sutures.

All animals were euthanized with an overdose of diethyl ether. Specimens were obtained at 2, 6, and 12 weeks postoperatively. The femora were excised, fixed in 10% formalin, decalcified in 5% formic acid, and embedded in paraffin. Sections (5 μm thick) parallel to the long axis of the femur were prepared and stained with H&E. Subsequently, histologic observations and histomorphometric analysis were performed under a light microscope.

One H&E-stained section was taken from the center of the resin cement. The following two measurements were performed using Image J.

L1: The peripheral length of the resin cement.
L2: The length of bone-cement in direct contact.

The means and standard deviations of the rates of bone-cement in direct contact (L2/L1)×100 [%] were calculated for each group. Differences among the groups were analyzed using the Tukey’s test; p-values < 0.05 were considered statistically significant. All statistical procedures were performed using Dr. SPSS II.

Moreover, the femora of Group GA+SB at 12 weeks (n=2) were cut using a precision sectioning saw (IsoMet® Low Speed Sow, BUHLER, Illinois, USA) in the middle of SB parallel to the long axis of the femur. The surface was polished, gold sputter-coated and observed under a scanning electron microscope (SEM, S-4000, Hitachi High-Tech Fielding Corporation, Tokyo, Japan). Specimens etched with a 6N aqueous solution of phosphoric acid (HCl) for 35 s and 10% NaOCl for 12 min were observed similarly.
RESULTS

EXPERIMENT 1

HISTOLOGIC OBSERVATIONS
At week 1, groups GA+SB and SB showed inflammatory cell infiltration consisting of mainly lymphocytes and few plasma cells and multinuclear giant cells (Fig. 1-a,b). Groups Pr+MB, MB and SX showed greater inflammatory cell infiltration consisting of similar cells than groups GA+SB and SB (Fig. 1-c,d). Additionally, groups Pr+MB and MB showed eosinophilic honeycombed layers inside MB close to the surface (Fig. 1-e).

At 2 weeks, every group showed less inflammatory cell infiltration than at week 1. Groups GA+SB and SB showed only a few scattered inflammatory cells near the surface (Fig. 2-a,b). Groups Pr+MB, MB and SX showed greater inflammatory cell infiltration than groups GA+SB and SB, although it was less than that at week 1 (Fig. 2-c–e).

HISTOMORPHOMETRIC ANALYSIS
The results showed that the extent of inflammatory connective tissue in groups GA+SB, SB, Pr+MB, MB and SX was 69.3±14.8 μm, 47.2±22.2 μm, 147.4±66.4 μm, 97.7±24.0 μm and 128.1±55.8 μm at week 1, and 36.8±15.4 μm, 20.3±10.3 μm, 70.4±26.2 μm, 36.3±29.1 μm and 70.5±30.6 μm at 2 weeks, respectively. Groups Pr+MB and SX exhibited a significantly larger extent compared to groups GA+SB and SB at week 1 (P<0.05). Groups Pr+MB and SX exhibited a significantly larger extent compared to groups GA+SB, SB and MB at 2 weeks (P<0.05). (Table 2)

EXPERIMENT 2

HISTOLOGIC OBSERVATIONS
At 2 weeks, SB was in direct contact with bone, although fibrous tissue had partially formed between bone and SB. A hematoxylinphilic layer was observed on the interface of bone in the area where SB was in direct contact with bone (Fig. 3-a,b). In the area where fibrous tissue had formed, several layers of fibroblasts and collagen fibers were observed between bone and SB (Fig. 3-c,d). In groups Pr+MB and SX, resin cement was rarely in direct contact with bone, and fibrous tissue had formed between bone and resin cement (Fig. 3-e–h). Newly formed bone was observed along the circumference of resin cement with fibrous tissue on the surface. Bone marrow tissue was partially observed between newly formed bone and cortical bone.

At 6 weeks, figures similar to those at 2 weeks were observed in group GA+SB. Although figures similar to those at 2 weeks were observed in groups Pr+MB and SX, newly formed bone had matured. Fat cells were observed in bone marrow tissue.

At 12 weeks, figures similar to those at 2 and 6 weeks were observed in group GA+SB. Although figures similar to those at 2 and 6 weeks were observed in groups Pr+MB and SX, the newly formed bone was partially unified with cortical bone (Fig. 4-c–f).

There were no disorders in the bone cells of cortical bone in groups GA+SB, Pr+MB and SX at any time point. Disappearance and atrophy of bone cells were not observed.

Table 2  Extent of inflammatory cell infiltration
Statistical analysis was performed by Tukey's test. All data are expressed as the mean ± standard deviation (μm).

*: p<0.05 (vs Pr+MB, SX)

<table>
<thead>
<tr>
<th></th>
<th>1 week</th>
<th>2 weeks</th>
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</thead>
<tbody>
<tr>
<td>Group GA + SB</td>
<td>69.3±14.8* (n=10)</td>
<td>36.8±15.4* (n=10)</td>
</tr>
<tr>
<td>Group SB</td>
<td>47.2±22.2* (n=10)</td>
<td>20.3±10.3* (n=10)</td>
</tr>
<tr>
<td>Group Pr + MB</td>
<td>147.4±66.4 (n=10)</td>
<td>70.4±26.2 (n=10)</td>
</tr>
<tr>
<td>Group MB</td>
<td>97.7±24.0 (n=9)</td>
<td>36.3±29.1* (n=10)</td>
</tr>
<tr>
<td>Group SX</td>
<td>128.1±55.8 (n=10)</td>
<td>70.5±30.6 (n=10)</td>
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Fig. 1 Histological findings of Experiment 1 at week 1 postoperatively (H&E staining)

a) Group GA+SB.
b) Group SB. 
Inflammatory cell infiltration consisting of mainly lymphocytes and few plasma cells (↑) and multinuclear giant cells (▼) was found near the surface of SB and connective tissue.
c) Group Pr+MB.
d) Group MB. 
Inflammatory cell infiltration consisting of mainly lymphocytes and few plasma cells (↑) and multinuclear giant cells (▼) was found to a larger extent than in groups GA+SB and SB near the surface of MB and connective tissue. There were eosinophilic honeycombed layers inside the MB near the surface.
e) Group SX. 
Inflammatory cell infiltration consisting of mainly lymphocytes and few plasma cells (↑) and multinuclear giant cells (▼) was found to a larger extent than in groups GA+SB and SB near the surface of SX and connective tissue. Collagen had disappeared. There were many erythrocytes.

Fig. 2 Histological findings of Experiment 1 at 2 weeks postoperatively (H&E staining)
a) Group GA+SB.
b) Group SB. 
Only few inflammatory cells were found scattered near the surface of SB and connective tissue. There was no disorder of the connective tissue (†) surrounding SB.
c) Group Pr+MB.
d) Group MB. 
The extent of the inflammatory cell infiltration was larger than in groups GA+SB and SB and was found near the surface of MB and connective tissue, although it was less than 1 week postoperatively. There were eosinophilic honeycombed layers inside MB near the surface.
e) Group SX. More and larger extent inflammatory cell infiltration than in groups GA+SB and SB was found near the surface of SX and connective tissue, although it was less than 1 week postoperatively.

Fig 3 Histological findings of Experiment 2 at 2 weeks postoperatively (H&E staining)
a) Group GA+SB. An area of SB was in direct contact with bone.
b) A higher magnification of the boxed area in (a). 
There was no fibrous tissue between SB and bone. A hematoxylinphilic layer (↑) was observed at the interface of bone.
c) Group GA+SB. Fibrous tissue was seen between SB and bone.
d) A higher magnification of the boxed area in (c). 
Several layers of fibroblasts and collagen fibers (▼) were observed between the bone and SB.
e) Group Pr+MB. 
f) A higher magnification of the boxed area in (e). 
MB was rarely in direct contact with the bone, and fibrous tissue was observed between bone and resin cement. Newly formed bone (*) was observed along the circumference of MB with fibrous tissue (▼) on the surface. Bone marrow tissue (†) was partially observed between newly formed bone and cortical bone.
g) Group SX. 
h) A higher magnification of the boxed area in (g). 
SX was rarely in direct contact with bone, and fibrous tissue was observed between bone and resin cement. Newly formed bone (*) was observed along the circumference of SX with fibrous tissue (▼) on the surface. Bone marrow tissue (†) was partially observed between newly formed bone and cortical bone.

Fig 4 Histological findings of Experiment 2 at 12 weeks postoperatively (H&E staining)
a) Group GA+SB. The part SB was in direct contact with bone.
b) A higher magnification of the boxed area in (a). 
There was no fibrous tissue between SB and bone. A hematoxylinphilic layer (↑) was observed at the interface of bone.
c) Group Pr+MB.
d) A higher magnification of the boxed area in (e). 
Fibrous tissue (▼) was observed between bone and MB similar to that at 2 weeks. Newly formed bone (*) had matured than at 2 weeks and partially unified with cortical bone. Fat cells were observed in bone marrow tissue (†).
e) Group SX. 
f) A higher magnification of the boxed area in (g). 
Fibrous tissue (▼) was observed between bone and SX similar to that at 2 weeks. Newly formed bone (*) had matured than at 2 weeks and partially unified with cortical bone. Fat cells were observed in bone marrow tissue (†).
HISTOMORPHOMETRIC ANALYSIS
The results showed that the rates of direct bone-cement contact in groups GA+SB, Pr+MB, and SX were 60.6±22.7%, 9.0±14.3% and 3.2±5.9% at 2 weeks, 66.2±22.7%, 10.0±24.5% and 2.3±3.6% at 6 weeks, and 55.3±30.5%, 8.8±9.5% and 2.5±4.1% at 12 weeks, respectively. Group GA+SB exhibited a significantly higher rate compared to groups Pr+MB and SX at 2, 6, and 12 weeks (P<0.05) (Table 3).

DISCUSSION

CONNECTIVE TISSUE REACTION
In experiment 1, connective tissue reactions to implanted resin cement were evaluated because resin cement affects not only bone but also connective tissue.

**Table 3** Rates of direct bone-cement contact
Statistical analysis was performed by Tukey's test. All data are expressed as the mean ± standard deviation (%).
*: p<0.05 (vs Pr+MB, SX)

<table>
<thead>
<tr>
<th>Group</th>
<th>2 weeks</th>
<th>6 weeks</th>
<th>12 weeks</th>
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<tbody>
<tr>
<td>Group GA+SB</td>
<td>60.6±22.7* (n=9)</td>
<td>66.2±22.7* (n=9)</td>
<td>55.3±30.5* (n=6)</td>
</tr>
<tr>
<td>Group Pr+MB</td>
<td>9.0±14.3 (n=10)</td>
<td>10.0±24.5 (n=6)</td>
<td>8.8±9.5 (n=9)</td>
</tr>
<tr>
<td>Group SX</td>
<td>3.2±5.9 (n=10)</td>
<td>2.3±3.6 (n=8)</td>
<td>2.5±4.1 (n=10)</td>
</tr>
</tbody>
</table>

**Fig. 5** SEM findings of group GA+SB at 12 weeks postoperatively
a) Group GA+SB.
b) A higher magnification of the boxed area in (a).

SB was in direct contact with bone in an extensive area. There was no gap between bone and SB.
c) Group GA+SB applied with HCl and NaOCl.

There was a 5-μm-thick layer that resisted HCl and NaOCl at the interface of bone.
when used as bone cement. Unreacted monomer, residues of initiator and accelerator have been identified as residues in the cured resins\textsuperscript{29,30}. The elution of these residues was considered the cause of tissue irritation. Moreover, adhesive resin cement needs surface treatment agents such as a conditioner or primer in order to attain high bond strength\textsuperscript{31,32}. Evaluation of cytotoxicity of these surface treatment agents are needed too. Thus, resin cements with or without surface treatment agents were used in this experiment.

The results showed minimal inflammatory cell infiltration in groups GA+SB and SB, whereas it was intense in groups Pr+MB and MB. The inflammatory cell infiltration in group Pr+MB was especially severe at week 1. Inflammatory cell infiltration in group SX was the same as the level in groups Pr+MB and MB.

The lower level of inflammatory infiltrate in groups SB and GA+SB than that in groups MB, Pr+MB or SX may be because SB uses TBB as initiator. It is known that residual MMA of the TBB-initiated polymerization resin is lower than one of the resins initiated by other initiators\textsuperscript{33}. Thus, in this experiment, the residual monomer of SB may be lower than MB or SX. Moreover, the monomer of MB contains UDMA which is more cytotoxic than MMA\textsuperscript{34}, and HEMA that causes sensitized delayed allergic reactions\textsuperscript{35,36}. The elution of these substances may induce more inflammation.

Inflammatory cell infiltration in group GA+SB was the same as in group SB. Thus, application of GA may not be very cytotoxic to connective tissue. GA, which is composed of 10\% citric acid and 3\% ferric chloride, shows strong acidity at pH 1\textsuperscript{32}. However, a short application time of 5 s and saline rinsing after application may contribute to a minimal inflammatory response. The inflammation in group Pr+MB was slightly more severe than that in group MB. Pr contains acetone, phosphoric acid monomer and UDMA\textsuperscript{34}. These residual substances may induce more inflammation.

BONE-CEMENT CONTACT

In group GA+SB, histologic observations showed that SB was mostly in direct contact with bone with no formation of fibrous tissue. SEM observations showed a 5-μm-thick layer that resisted HCl and NaOCl at the interface of bone. This layer may possess the same structure as the hybrid layer observed on the interface of dentin and adhesive resin cement\textsuperscript{28}. SB adhered to bone demonstrated the hybrid layer. The rates of direct bone-cement contact in group GA+SB were at the same level at every time point. Multinuclear giant cells were not observed near the SB and bone interface. Therefore, the contact of SB and bone exhibited long-term stability.

One advantage of SB may be where the initiation starts. TBB requires water and oxygen to form radicals which initiate the polymerization on tissue surface\textsuperscript{38}. Because the intramedullary canals consist of comparatively much water and blood, initial polymerization may start at the bone surface in group GA+SB. The initial polymerization at the bone and SB interface may enhance adhesion and prevent formation of fibrous tissue.
Although an adhesion monomer is used in group Pr+MB, formation of fibrous tissue between MB and bone was mostly observed. The borate catalyst included in MB requires acid to form radicals which initiate the polymerization. This means initiation starts at the surface to which Pr consisting of acid monomer is applied.

However, Pr may be buffered by water and blood at the bone surface. Thus, the polymerization on the surface may be inhibited and fibrous tissue may form between MB and bone.

Formation of fibrous tissue between SX and bone was mostly observed as well. An adhesion monomer which infiltrates bone is not used in group SX. Moreover, when the initiation system such as BPO/DMPT is used, shrinkage occurs toward the center of the resin, whereas when a chemically activated initiation system such as TBB or borate catalyst is used, polymerization will proceed outward from the interface. Thus, a gap would be formed between bone and resin cement and fibrous tissue may form into the gap.

**BONE REACTION**

The inside of intramedullary canals was stimulated by curettage, drying and application of the resin cement. However, disorders of the bone tissue or bone cell were not observed in any group at any time point, even in the area of bone in contact with SB. Thus, SB has no cytotoxicity to bone cells when in contact with bone.

With less inflammatory reactions, high rates of direct bone-cement contact and bone stability, 4-META/MMA-TBB would be of great benefit in orthopedic surgery and loosening of fixed biomaterials can be reduced using this cement. Further investigations are required to determine the bond strength for bone cement to fix prostheses, and the stability of contact in the case of functional stress.

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