Tissue reaction around loosened prostheses: a histological, X-ray microanalytic and immunological study.

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Abstract

Tissue reactions at the cement-bone and artificial implant-bone interface were examined light and electron microscopically in thirty-six patients who underwent revisory operation of hip or knee replacement. The reactions were classified into three types: inert tissue, active tissue with giant cell proliferation, and active tissue with predominant foamy cell proliferation. The third type of reaction was found only in total hip replacement with bone cement. No evidence of allergic reaction to implanted materials was found in any replacement, though active cellular infiltrations were observed around loosened prostheses especially in cemented arthroplasty. The tissue reactions always occurred around instable or loosened prostheses. Thus, the present study shows that mechanical instability is the primary cause of such undesired tissue reactions.

KEYWORDS: loosening, replacement arthroplasty, bone cement, foreign body reaction, metallic deposit

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Tissue Reaction around Loosened Prostheses: A Histological, X-Ray Microanalytic and Immunological Study

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Tissue reactions at the cement-bone and artificial implant-bone interface were examined light and electron microscopically in thirty-six patients who underwent revisionary operation of hip or knee replacement. The reactions were classified into three types: inert tissue, active tissue with giant cell proliferation, and active tissue with predominant foamy cell proliferation. The third type of reaction was found only in total hip replacement with bone cement. No evidence of allergic reaction to implanted materials was found in any replacement, though active cellular infiltrations were observed around loosened prostheses especially in cemented arthroplasty. The tissue reactions always occurred around instable or loosened prostheses. Thus, the present study shows that mechanical instability is the primary cause of such undesired tissue reactions.

**Key words:** loosening, replacement arthroplasty, bone cement, foreign body reaction, metallic deposit

It is generally accepted that aseptic loosening of components after hip and knee joint replacement is one of the main factors causing severe failure (1-5). Although the loosening is indicated by a radiolucent line, the radiolucency is not always related to the clinical failure (6). However, the loosening can be clinically troublesome when the radiolucent line is wider than two millimeters and irregular with some sort of bony absorption. Many hypotheses have been proposed with regard to the etiology of the loosening: mechanical factors (5), granulomatous reaction caused by excessive wear products at the articulating surfaces (4,5,7-11), and vasculitis caused by allergic reactions to the implanted materials (12).

In this study, we investigated further details of the tissue reactions at the loosened cement-bone and artificial implant-bone interface, and revealed that mechanical instability is the main reason for loosening of prostheses both with and without cement, though tissue reactions differ somewhat in each case.

**Materials and Methods**

*Patients.* Thirty-six patients underwent surgical revision of replacement arthroplasties after clinical failure. Fifteen patients (fifteen hips) underwent re-operations after total hip replacement (THR) using bone cement (CMW, made by Howmedica International Ltd.); five patients (five hips) underwent surgery after hemiarthroplasty with an Austin-Moore prosthesis without bone cement; six patients (six hips) underwent THR to salvage a cup arthroplasty, and ten patients (eleven knees) underwent surgery to revise a total knee replacement (TKR) without cement.

*Tissue sampling and processing.* In each re-
operation, small tissue samples were obtained from various areas of the cement-bone or artificial implant-bone interfaces around the capsule and socket of the prostheses. The tissue fragments were fixed in 10% formalin in 0.1 M phosphate buffer (pH 7.2), embedded in paraffin, cut into sections of 3 μm in thickness, and stained with hematoxylin-eosin. The sample sections with dark brown deposits were stained with a mixture of 2% K$_4$Fe(CN)$_6$ and 1% HCl for Prussian blue stain to detect metal (iron) deposits. Foreign bodies were examined under a polarized light microscope (Optiphot-Pol, Nikon Co., Ltd.). Oil red O stain was used to detect lipid deposits. Immunological assay of lysozymes and globulins was performed by the peroxidase antiperoxidase (PAP) method (13).

Some tissue samples from three cases of THR were fixed in 2.5% glutaraldehyde in 0.1 M phosphate buffer (pH 7.2), post-fixed in 1.0% osmium tetroxide in 0.1 M phosphate buffer (pH 7.2). They were embedded in an epoxy resin, cut into ultrathin sections (silver-gray), and surveyed by an electron microprobe analyzer (H-800, Hitachi Co., Ltd. & Kevex) to examine metal content. Some of these sections were stained with uranyl acetate and lead acetate and observed with a transmission electron microscope (002A, Akashi Co., Ltd.).

Results

Light microscopy of hematoxylin-eosin stained sections showed that the tissues around the loosened prostheses with or without cement could be classified into three types: inert tissue, active tissue with giant cell proliferation, and active tissue with predominant foamy cell proliferation. The inert tissue contained few capillaries and mainly consisted of fibrous elements and fibroblasts, resembling loose connective or synovial tissue (Fig. 1). In contrast, the active tissues contained many capillaries and also many giant or foamy cells in addition to histiocytes and foreign bodies. The giant cells were characterized by their extraordi-

Fig. 1 Membranous tissue around the stem of Austin-Moore prosthesis, hematoxylin-eosin. A: Loose connective tissue with mild vascular invasion and fibroblast proliferation, ×50. B: Higher magnification of the mid-part, ×250.
narily large size compared with fibroblasts and histiocytes, and the foamy cells were characterized by the vacuolations of their cytoplasm. These active tissue reactions were typically observed in the mid-portion of the interface between the implanted prostheses and the bony tissues. The details of the active reactions are described below together with those obtained by transmission electron microscopy, polarized microscopy,

**Table 1** Pathological findings of the tissues around prostheses without cement

<table>
<thead>
<tr>
<th>Type of prosthesis</th>
<th>Tissue examined</th>
<th>Total number of examined cases</th>
<th>Cases with dominant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Giant cell</td>
</tr>
<tr>
<td>Austin-Moore prosthesis</td>
<td>Capsule</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Total hip prosthesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cup arthroplasty</td>
<td>Capsule</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Total hip prosthesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee prosthesis</td>
<td>Capsule</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>without cement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee prosthesis</td>
<td>Femoral side</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Tibial side</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

*Fig. 2* Large foreign bodies are birefringent under polarized light. A: Capsule around loosened prosthesis with cement contains large foreign bodies, ×500. B: The foreign bodies are also found in tissue surrounding loosened total knee replacement (TKR) without cement, ×25.
Fig. 3 Microscopic findings in cases with giant cell proliferation at the tissue reaction site. A: Tissue was taken from around loosened stem of Charnley prosthesis in a 62-year-old woman, hematoxylin-eosin, ×120. B: Higher magnification of a part of A, showing phagocytized foreign bodies in a giant cell, hematoxylin-eosin, ×250. C: Sectioned samples were taken from the high density polyethylene-bone interface from the revised knee prosthesis without cement of an 84-year-old man. Large foreign bodies are shown in this tissue, hematoxylin-eosin, ×25. D: Accumulation of foreign body giant cells is shown in the same sample of C, hematoxylin-eosin, ×120.
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Tissue Reaction around Loosened Prostheses

metallic analysis and immunological reaction.

In the prosthetic replacements without cement, such as hemiarthroplasty with Austin-Moore prostheses or cup arthroplasty, resected tissues around prostheses rarely had histiocye proliferation due to reaction with foreign bodies (Table 1). In the revision cases of TKR without cement, no foamy cells were found (Table 1). Histology of the capsules from six TKR cases showed that giant cells proliferated in one case and that foreign bodies were deposited in three cases. On the femoral side of seven cases, giant cells were found in two cases and extracellular foreign bodies in two cases. In the tibial side samples of nine cases, numerous giant cells having large foreign bodies (Fig. 2-B) were found in two cases. Deposits of only foreign bodies were seen in four cases. There seemed to be little relationship between the appearance of foreign bodies and active tissue reactions (Fig. 3). In two revised TKR cases, a number of high density polyethylene flakes were observed in giant cells which predominantly infiltrated the surrounding tissue (Figs. 2-B and 3-C,D). Large high density polyethylene flakes with birefringency (2-1000 μm) were also found in giant cells which predominantly appeared in the tissue reaction in three cases of THR revisions (Fig. 2-A) and two cases of TKR revisions (Fig. 2-B).

In cemented THR, light microscopy and polarized microscopy of hematoxylin-eosin stained sections showed deposits of birefringent foreign bodies and predominant giant cell proliferation on the socket side in two of eight hips of which samples were obtainable. Foamy cells were found in three cases. In the capsules of fourteen cases examined, giant cells were found in three cases, foamy cells in six cases and foreign bodies in seven cases. In stem side samples from ten cases, giant cells were observed in two cases, foamy cells in six cases and foreign bodies in five cases. Foamy cells and foreign bodies on the stem side were found in one and half times more frequently than on the socket side (Table 2). However, there was no relationship between the appearance of foamy cells and that of foreign bodies.

Foamy cells (Fig. 4) were detected only in the tissues from revision of THR with bone cement. Foamy cells phagocytized very small birefringent granules under the polarized light microscope (Fig. 5-A). In one of the specimens that showed the foamy cell predominant tissue reaction, a large birefringent substance (about 60 μm × 40 μm in size) was found in the foamy cell sheet (Fig. 5-B). The birefringency was the same as that of the cytoplasm of the foamy cells. Neutrolipid granules were detected in the cytoplasm of foamy cells with oil red O stain (Fig. 6).

By transmission electron microscopy, these cells were observed to contain many septate vacuolar phagosomes (about 0.2 μm to 3.0 μm in size) which enclosed high density polyethylene flakes (Fig. 7-A). Most

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</tr>
</thead>
<tbody>
<tr>
<td>Total hip prosthesis</td>
<td>Socket side</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Capsule</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Total hip prosthesis</td>
<td>Stem side</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
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Fig. 4  Histology of tissue surrounding the revised total hip replacement (THR) on the stem side of a 55-year-old man with severe loosening after THR.  A: Proliferation of foamy cells is marked, hematoxylin-eosin, $\times 120$.  B: Higher magnification of a part of A showing the accumulation of foamy cells with dense cytoplasm, hematoxylin-eosin, $\times 370$.  C: Higher magnification of a part of A showing foamy cells with rather clear cytoplasm, hematoxylin-eosin, $\times 250$.  D: Mononuclear histiocytes surround a foreign substance, hematoxylin-eosin, $\times 500$. 

http://escholarship.lib.okayama-u.ac.jp/amo/vol40/iss5/1
Fig. 5  The same sections as in Fig. 4, seen under polarized light. A: Birefringent granules are shown in the cytoplasm of foamy cells, ×600. B: The substance surrounded by the histiocytes is birefringent as is the cytoplasm of foamy cells shown in A, ×1,200.

Fig. 6  Samples were taken from the cement-bone interface in the stem side of a 63-year-old woman with severe loosening. A: Proliferation of foamy cells is marked, hematoxylin-eosin, ×250. B: Neutrolipids were demonstrated in the cytoplasm of foamy cells by oil red O stain, ×250.
Fig. 7  Electron micrograph of foamy cell in the tissue around a loosened Charnley prosthesis. A: Many vacuolar phagosomes, which each have an intravacuolar septum (arrows), are found in the cytoplasm; N, nucleus; \( \times 8,700 \). B: Unidentified granular particles seem to be bone cement, but are not identified (arrows); N, nucleus; \( \times 10,800 \).
of the other substances in the phagosomes were unidentified, although the small granular particles seemed to correspond to cement particles (Fig. 7-B).

Weak staining of lysozyme was demonstrated in the cytoplasm of histiocyte-like cells at the cement-bone interface by the PAP method (Fig. 8). Plasma cells were rarely found in any of the specimens. Positive staining of immunoglobulins (IgG, IgA and IgM) was not demonstrated by the PAP method even in samples with active tissue reactions showing histiocyte proliferation.

Dark pigments reactive with the Prussian blue stain were sometimes found in the cytoplasm of histiocytes and intercellular spaces in one THR case and two TKR cases (Fig. 9-A).

By transmission electron microscopy, dense granules of various forms (0.2 μm-2.0 μm in size) were noted in the cytoplasm of the foamy cells (Fig. 9-B).

Electron microprobe analysis of the dense granules in the cytoplasm confirmed that the granules contained chromium, nickel, cobalt, iron and titanium (Fig. 10).

Discussion

It is well known that a distinct clear zone thicker than 2 mm is observed roentgenographically between loosened prostheses and the surfaces of bony tissues. Linder et al. (5) histologically classified the tissues of this clear zone into three types in their study of loosened total hip replacements with cement; namely, densely fibrous tissue, loose connective tissue with many small and medium sized vessels, and loose connective tissue dominated by fat-laden macrophages. Goldring et al. (14) also studied histologically loosened total hip replacements and proposed...
Fig. 9  Light (A) and electron micrographs (B) of the granulated tissue at stem side of a 47-year-old man with severely loosened total hip replacement (THR). A: Pigmented substances are found in the cytoplasm of a mononuclear histiocyte, Hematoxylin-eosin, ×760. B: Various forms of dense granules are found in the cytoplasm (arrows) corresponding to metal substances, ×13,300.
Fig. 10 Microprobe analysis of dense granules in the cytoplasm shows them to contain Cr, Ni, Co, Fe, and Ti, which are the same as the materials of the Charnley prosthesis.

a more reasonable classification, taking the zonation properties into consideration: synovial-like layer of lining cells at the cement surface, sheets of histiocytes and giant cells in the mid-portion, and a fibrous layer that blended into the bone. The present study extended the studies of the previous authors and revealed that the mid-portion described by Goldring and his associates can be further classified into three types according to the dominant cell types: inert tissue mainly containing fibroblasts, active tissue with giant cell proliferation, and active tissue with predominant foamy cell proliferation.

At the mid-portion of membranous granulation in an active reaction with giant cell proliferation, a large number of birefringent foreign bodies can be observed. Such abundant foreign body depositions, clearly identified as flakes of high density polyethylene under polarized light, could be a main factor causing active tissue reaction with giant cell proliferation. However, it is difficult to elucidate whether the form of tissue reaction is related to the volume of foreign bodies or to the phase of the reaction, and whether active tissue reaction with giant cell proliferation leads to more giant cell proliferation rather than foreign body production (15).

It is generally accepted that mononuclear histiocytes are converted into foamy cells which phagocytize tiny substances such as necrotized products and foreign bodies. The present polarized light microscopic study showed that foamy cells in tissue with foreign body deposits contain small birefringent granules in the cytoplasm. Charnley (16) indicated that such birefringent particles were wear products from the high density polyethylene, but some authors (3, 4, 17) have reported that methylmethacrylate of the bone cement has birefringency. Freeman et al. (7) have reported that numerous macrophages are present in the tissue around total knee prosthesis with cement. In this study, the active tissue reaction with proliferation by numerous foamy cells was found only in the tissue from revised THR, and was not recognized in the tissue from revised TKR without cement. Therefore, foamy cells predominante in active reactions found in the tissue surrounding cemented prostheses.

Some authors (4, 10, 18) suggested the possibility that the methylmethacrylate of the bone cement might be modified in living tissue. The substances surrounded by mono-
nuclear histiocytes as shown in Figs. 4 and 5 seem to be altered methyImethacrylate, because they have the same birefringency that the cytoplasm of foamy cells has. In the cases of revised THR, numerous foamy cells contained birefringent substances in their cytoplasm, even in the specimens covering the back of the socket. Therefore, the birefringent substances in the foamy cells appear to be altered methyImethacrylate of bone cement.

The type of tissue reaction seemed to be decided by the volume or size of the foreign bodies. Our results indicated that large foreign bodies such as flakes of high density polyethylene induce giant cell proliferation, while very small substances such as altered fragments of bone cement produced foamy cell proliferation.

In our observations, weak positivity of lysozyme was detected by the PAP method (13) in the foreign body giant cells and foamy cells, but such histiocytes may exhaust the enzyme during the phagocytosis of the particles. Nevertheless, lysozyme in proliferated histiocytes, such as foreign body giant cells or foamy cells, might cause osteolysis found in loosened THR. Freeman et al. (7) also indicated that macrophages can be responsible for bone absorption in the clear zone in cemented TKR.

Christiansen et al. (12) suspected allergy of the implanted materials to the surrounding tissue. However, this study provided no histological evidence of participation in hypersensitivity of implanted materials to the tissue such as vasculitis, eosinophilia or deposition of immunoglobulin.

In our examination, metallic deposits were found in one of fifteen cases of THR revision (6.7%), and two of eleven TKR revisions (18.2%). Johnston (8) stated that metallic deposits appeared in sixteen percent of Charnley prostheses. The metallic deposits were found in very small granules of the mono-
nuclear histiocytes in our ultrastructural study. Electron microprobe analysis confirmed that granules contained the same contents as the prosthetic metals. It could not be decided, however, whether the metal deposit was produced by mechanical wear or metal corrosion due to some kind of tissue reaction.

As reported by Linder et al. (5), regarding the mechanism of prosthetic loosening, mechanical instability was assumed to be the primary cause of the tissue reaction, because surrounding tissue was inert at the early stage of the loosening, and active tissue reaction occurred as a result of instability of the inserted prosthesis. Our study also confirmed that a mild foreign body reaction showing fibrous membrane around the prosthesis can occur with a rather stable prosthesis, such as Austin-Moore or cup arthroplasty. On the other hand, instable prostheses with or without cement can produce much wear debris at the articulation during motion, and such wear debris of rather large high density polyethylene flakes can induce giant cell proliferation. Furthermore, tiny cement debris can also be produced at the cement-bone interface, and induce predominant proliferation of foamy cells as shown in this study. Massive proliferation of giant cells and foamy cells containing lysosomal enzymes can introduce resorption of bony structure, causing extensive loosening of the prosthesis.

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