HYPERSENSITIVITY IN ASEPTIC LOOSENING OF TOTAL HIP REPLACEMENTS
THE ROLE OF CONSTITUENTS OF BONE CEMENT

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Aseptic loosening is seen in a significant proportion of cemented total hip replacements (THR). In a small subgroup of patients who suffer early loosening polyethylene debris is unlikely to be responsible. We recently reported one case of allergic contact dermatitis to N,N-dimethylparatoluidine (DMT), an accelerator used in bone cement. We have therefore investigated this using skin-patch tests to a variety of substances including metals, polyethylene and the separated individual components of Simplex cement.

We studied 70 patients, 15 with aseptic loosening less than two years after THR, 25 with satisfactory long-term cemented fixation, five with infected loosening of cemented THRs and 25 awaiting hip arthroplasty. We found seven positive reactions to DMT, all of them in patients with the rapid onset of aseptic loosening.

Allergy to DMT is recognised in the dental profession in respect of the ‘denture sore mouth’ syndrome, and could also be an occupational hazard since some industrial glues contain DMT. Our results suggest the need for awareness of possible previous dental or occupational exposure to the constituents of bone cement. We recommend the use of skin-patch testing in high-risk cases.

Received 9 May 1995; Accepted after revision 15 February 1996

Aseptic loosening remains the most common complication after total hip replacement. Mechanical factors are considered to be principally responsible (Charnley 1979; Jasty et al 1991), but biological reactions to implanted foreign material may have an important role (Sutherland et al 1982; Jasty et al 1986). Debate continues about the interface which is primarily affected (Gardiner and Hozack 1994). The role of debris, and particularly of polyethylene wear fragments, in the development of loosening is well established (Goldring, Clark and Wright 1993). There remains, however, a small subgroup of patients with very early loosening in whom polyethylene debris is unlikely to be responsible (Jones and Hungerford 1987).

We have recently reported one such patient who was shown to be allergic to a constituent of bone cement (N,N-dimethylparatoluidine; DMT) on skin-patch testing (Haddad et al 1995). We have now used skin-patch tests to assess allergic responses in patients with rapid aseptic loosening and to compare them with those in patients with a satisfactorily fixed or a loose THR, patients awaiting their first THR, and normal control subjects.

PATIENTS AND METHODS

We studied a total of 70 patients who were assessed by an orthopaedic surgeon and a dermatologist, and had radiography. We excluded those with a history of atopy because they would have a higher risk of unrelated positive reactions. Radiological loosening was defined as the presence of a complete lucent line wider than 2 mm at one of the interfaces. The patients were divided into four groups as follows (Table I):

Early loosening. There were 15 patients, eight female and seven male, with an average age of 69 years. They had had Stanmore (Biomet, Bridgend, UK) or Charnley (DePuy, Leeds, UK) cemented THRs at the Royal National Orthopaedic Hospital, using Simplex (Howmedica, London, UK) cement and second-generation cementing techniques. All had satisfactory postoperative radiographs. None had wound infections or subsequent trauma to the replaced hip, but developed symptoms and radiological loosening within two years requiring revision arthroplasty. At revision, both components of the THR were loose in all 15 patients. None had clinical or serological indication of infection, and fluid from joint aspiration and tissue samples taken at revision...
were all sterile. Radiographs of one patient are shown in Figures 1 and 2.

Satisfactory fixation at five years. We reviewed and tested 25 patients who had had cemented Stanmore or Charnley THRs at the Royal National Orthopaedic Hospital, using identical techniques. All had a satisfactory clinical and radiological result after at least five years (mean 67 months).

Control group. This group comprised 25 otherwise normal patients awaiting THR.

Infected loosening. We studied five patients who had loosening of infected cemented THRs using the same cement.

The four groups were well matched for age, gender, body-weight, activity level and general medical conditions.

Skin-patch tests were used to investigate any allergic reactions to the implanted foreign materials. Patch testing was performed on the patient’s back, using a standard battery of materials which included chromium, nickel, cobalt, titanium, polyethylene and the separate individual components of Simplex cement (Table II). The test sites were examined and graded at 48 and 96 hours by a dermatologist. A positive result required palpable erythema at both 48 and 96 hours. The clinician assessing the patch-test result did not know the patient’s surgical history.

RESULTS

Reactions to the standard battery of tests were evenly distributed between the four groups. They included reactions to formaldehyde, Primin, benzocaine, thiuram, epoxy resin and black rubber mix. We could find no discernible

Table I. Details of patient groups and summary of patch test results

<table>
<thead>
<tr>
<th></th>
<th>Early aseptic loosening (n = 15)</th>
<th>Stable THR (n = 25)</th>
<th>Awaiting THR (n = 25)</th>
<th>Infected THR (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (range)</td>
<td>69 (58 to 75)</td>
<td>67 (51 to 75)</td>
<td>69 (59 to 73)</td>
<td>71 (61 to 78)</td>
</tr>
<tr>
<td>Male:female</td>
<td>7:8</td>
<td>12:13</td>
<td>11:14</td>
<td>1:4</td>
</tr>
<tr>
<td>Reaction to standard battery</td>
<td>7</td>
<td>0</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Reactions to metals</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reactions to methylmethacrylate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reactions to DMT</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

![Figure 1](image1.png)  
![Figure 2](image2.png)  

Figure 1 – The right hip of a 73-year-old man three months after a standard primary Stanmore cemented THR. Figure 2 – The same hip one year later, showing significant lysis around the loose components.
pattern to these reactions. There was no hypersensitivity to polyethylene, any of the metals, methylmethacrylate, benzoyl peroxide or hydroquinone. We found seven positive reactions to DMT and all of these were in the 15 patients in the early loosening group (Table I). The chi-squared test with Yates’ correction and one degree of freedom showed highly significant differences (p < 0.001) between the early loosening group, the group with satisfactory THRs, and the control group. Because of the small number the difference between the aseptic and infected groups was not significant (p < 0.25).

DISCUSSION

Studies of the cement-bone interface of THRs have shown that a synovium-like membrane forms which has the capacity to produce prostaglandin E₂, collagenase and other osteolytic products such as interleukin-1 and tumour necrosis factor (Eskola et al 1990; Horowitz et al 1993). The macrophage/giant-cell reaction has been likened to type-IV hypersensitivity, but it is not clear whether this is a primary or a secondary phenomenon. Intensive searches for allergens have been made and high concentrations of cobalt, chromium and nickel, particularly from metal-to-metal prostheses, have been implicated (Evans et al 1974; Benson, Goodwin and Brostoff 1975). Titanium sensitivity has recently been proposed (Lalor et al 1991). Bone cement has also been studied, since many cases of allergic contact dermatitis have been reported in dental surgeons, operating-theatre staff and orthopaedic surgeons (Pegum and Medhurst 1971; Fries, Fisher and Salvati 1975). Methylmethacrylate is known to be an allergen in a small percentage of the population (Cavelier et al 1981), but it has not yet been possible to establish a link between this hypersensitivity and aseptic loosening after THR (Waterman and Schrick 1985). Little attention has been paid to the effects of the other components of bone cement.

The curing of bone cement involves the induction of polymerisation at room temperature of a mixture of methylmethacrylate monomer and polymethylmethacrylate powder using benzoyl peroxide as an initiator, hydroquinone as a stabiliser and DMT as an accelerator. DMT is an aromatic tertiary amine which causes rapid decomposition of the peroxide initiator to form a large number of free radicals, and is present in varying concentrations in all the commonly used bone cements. We used a 0.5% concentration of DMT for skin testing. This compares with 2.13% in Palacos cement and 2.48% in Simplex cement before mixing. Polymerisation of bone cement is rarely complete: some free DMT remains in the final compound (Trap, Wolff and Jensen 1992) and this could be responsible for a hypersensitivity phenomenon.

Hypersensitivity to DMT has aroused some interest in the dental literature in respect of contact stomatitis and the ‘denture sore mouth’ or ‘burning mouth’ syndrome (Kaaber, Thulin and Nielsen 1979; Tosti et al 1990). The dental use of acrylic cements which contain aromatic amine accelerators has now decreased for a variety of reasons, but a large number of patients have been exposed to DMT and possible sensitisation.

The possible role of DMT hypersensitivity in aseptic loosening of joint replacements has also important occupational implications. There may be significant previous exposure to DMT in workers using industrial glues and in surgeons, dentists and operating-theatre staff. Such sensitisation may render these groups of the population more susceptible to the rapid failure of cemented arthroplasties. At least two of our early loosening group were carpenters who had contact with industrial glues.

Our results suggest that DMT hypersensitivity is an indicator of rapid aseptic loosening. We cannot ascertain from this limited study whether this is a primary phenomenon or secondary to the onset of loosening. Our negative results in patients with septic loosening suggest that it may be primary, and this is further supported by the fact that all three patients with DMT hypersensitivity who had a cemented revision hip arthroplasty had repeated rapid failure by aseptic loosening.

Hypersensitivity to DMT may contribute to the early and catastrophic loosening of some cemented total hip replacements; we have identified a simple minimally invasive test which can distinguish some patients who are likely to have such loosening. An important issue is possible sensitisation due to previous dental or occupational exposure to this DMT, and another is the type of revision surgery used after early loosening. We are continuing studies to elucidate the precise role of allergic phenomena in early aseptic loosening, but suggest the use of skin-patch testing for patients considered to be at risk of sensitivity.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

REFERENCES


