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Patient Sensitivity to Polyethylene Particles with Cemented Total Hip Arthroplasty

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Abstract: To determine whether sensitivity to polyethylene particles varies among patients, we studied 25 patients who had undergone total hip arthroplasty. We used pelvic radiographs to measure annual polyethylene wear and the area of osteolysis. The ratio of the area of osteolysis to the volumetric polyethylene wear was defined as sensitivity index. Adherent cells from peripheral blood were cocultured with polyethylene particles, and the amount of bone-resorptive cytokines was measured. The amount of interleukin-6, but not of interleukin -1β or tumor necrosis factor-α, released from adherent cells in the in vitro experiment correlated with the in vivo sensitivity indices. This technique appears capable of predicting the development of polyethylene-induced osteolysis, allowing surgeons to avoid using polyethylene as the bearing surface in patients at risk for osteolysis. **Key words:** total hip arthroplasty, polyethylene-induced osteolysis, sensitivity index, interleukin-6, prevention.

The long-term results of total hip arthroplasty (THA) continue to improve [1,2]; however, many problems remain to be resolved, including periprosthetic osteolysis with subsequent loosening of the prosthesis [3].

Although there is some experimental evidence that osteolysis is induced by increased intra-articular joint pressure [4], osteolysis is also thought to follow a biologic pathway [5]. There are several reasons for this: (1) the more the acetabular polyethylene wears down, the more frequently periprosthetic osteolysis occurs [6]; (2) a study on in situ hybridization has shown that the presence of cytokines such as interleukin (IL)-1β, IL-6, and IL-8 and tumor necrosis factor (TNF)-α in the soft tissue of joints with loose prostheses [7]; (3) cytokines (such as IL-1β and IL-6), TNF-α, and prostaglandin E_2 are released by the effects of various particles on human macrophages or macrophagelike cells in vitro [8]; and (4) osteoclastogenesis is not induced in TNF receptor–deficient mice exposed to polymethylmethacrylate particles [9].

This biologic pathway is considered to follow processes when the bearing surface between the socket and head is worn and numerous polyethylene particles are generated. These particles are phagocytosed by macrophages, and the activated macrophages then release various bone-resorptive cytokines. These cytokines enhance osteoclastogenesis directly or indirectly via the receptor activator of the nuclear factor κB (RANK)-RANK ligand (RANKL) signaling pathway [10], and thus periprosthetic bone is resorbed.

However, extraordinary variations in the degree of osteolysis are sometimes encountered. Some patients have little wear of the polyethylene but

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show massive osteolysis, whereas others have severely worn polyethylene but do not show osteolysis. Some reports have focused on whether an individual's allergic hypersensitivity to metallic devices is related to periprosthetic loosening [11,12]. The existence of patient sensitivity to particulate debris is suggested in a standard textbook [13]. However, this has not been supported by experimental data, so the controversy remains unresolved.

We measured the ratio of the area of osteolysis to the volumetric polyethylene wear by using radiographs obtained from patients during long-term follow-up who did not have prosthetic loosening. We also measured the levels of bone-resorptive cytokines in culture supernatants from adherent cells (macrophages) obtained and differentiated from the peripheral blood of these patients. These were cultured with polyethylene particles separated from the periprosthetic tissue of other patients. We then analyzed any relationships among the data.

Materials and Methods

The ethics committee of Kyoto University approved this clinical study. All patients consented to participation after being informed of the study's purposes, methods, and risks.

Patient Selection

Twenty-five women with osteoarthritis participated in this study. Their mean age at surgery was 52.0 years (range, 37.0-66.0 years), and the mean length of the follow-up period was 13.7 years (range, 7.1-21.5 years).

Twenty-two hips underwent alumina ceramic-on-polyethylene THA (Bioceram and KC series, Kyocera, Kyoto, Japan), and 3 hips underwent metal-on-polyethylene THA (original Charnley, Thackray, Leeds, United Kingdom). The inner head diameters of the alumina-on-polyethylene prostheses were 22.225 mm in 8 hips, 26 mm in 1 hip, and 28 mm in 13 hips. The inner head diameter of the metal-on-polyethylene prostheses was 22.225 mm in 3 hips. The acetabular sockets were fixed with bone cement (CMW1, CMW Laboratories, Devon, United Kingdom). The stems were also fixed with bone cement (CMW3, CMW Laboratories) applied using a cement gun, with the so-called second-generation technique. All bone cement/prosthesis interfaces in the femur were rated as grade A using the criteria of Barrack et al [14]; no radiolucent lines were seen at the bone cement/prosthesis interfaces in the acetabulum. At the final follow-up examination, no prostheses were aseptically loose, although massive osteolysis was observed in some.

Radiologic Analysis of Polyethylene Wear

Polyethylene wear was radiologically measured by determining the migration of the center of the inner head relative to the center of the socket, using the computer-aided technique described by Tanaka et al [15]. The analytic tools used in this study, including digitized radiographs and software, were as previously reported [15]. For each patient, a series of annual pelvic radiographs were selected and digitized using an image scanner (GT-9500, Seiko Epson, Nagano, Japan). After 10 points around the periphery of the inner head and the cement-polyethylene socket interface had been identified in each radiograph, image analysis software (Image-Pro Plus, version 4.0, Media Cybernetics, Bethesda, Md) identified best-fit circles and their centers. By comparing the coordinates of the centers on each radiograph, we determined the amount and the direction of penetration of the inner head into the socket, after correcting for pelvic tilting and magnification. Volumetric wear was calculated by using the equation described by Hashimoto et al [16].

Radiologic Analysis of the Area of Osteolysis

The areas of osteolysis were measured radiologically by determining the edges of the osteolytic lesion. The area was defined according to the criteria of Devane et al [17] as a progressive radiolucent, expansive, or linear area surrounding the prosthesis or cement. For each patient, a series of annual pelvic radiographs were selected and digitized using an image scanner (Scion Image, version 4.0.2; Scion, Frederick, Md) to generate 72-dpi images (tagged image file format) that recorded the areas of osteolysis, as shown in Fig. 1.

Reliability of Measurements

To validate this measurement, 2 of the authors (KI and KK) measured the total volumetric wear and the area of osteolysis in a blinded fashion. For 10 randomized selected cases, the measurements were repeated 3 times at 1-week intervals to assess intraobserver reliability.

Preparation of Polyethylene Particles

Polyethylene particles were isolated from periprosthetic tissues obtained during revision surgery from 4 patients who had undergone primary cemented THA using an original Charnley prosthesis. Using the method described by Minovic et al [18],

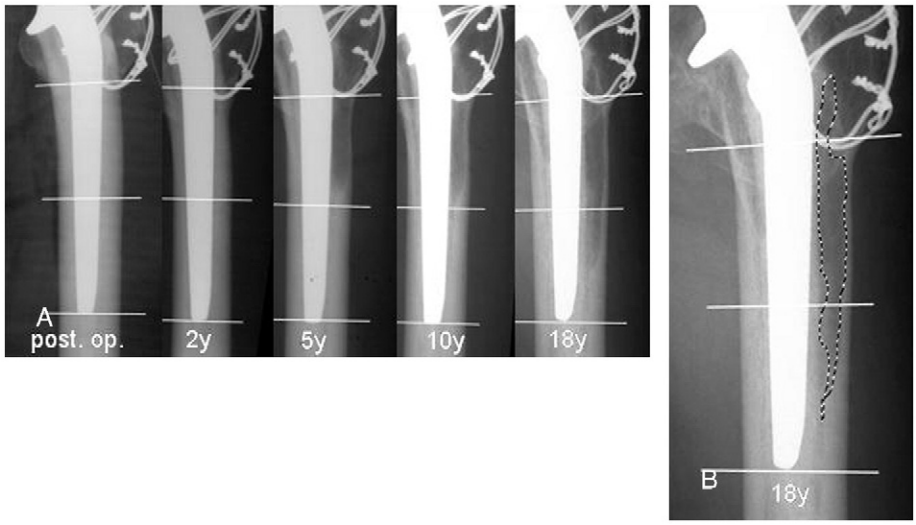

Fig. 1. Radiologic evaluation of osteolytic lesions using plain radiographs. Clinical course of the area of osteolysis (A). Area of osteolysis was determined from the edge of the osteolytic area using analysis software. Area surrounded by the dotted line is the measured area of osteolysis (B).

we minced periprosthetic tissues and immersed them in a 2:1 chloroform-methanol solution overnight, and then immersed them in xylene for 5 hours. After we rinsed them with distilled water, about 5 g of tissue was placed into a tube, 12 mL of 5 mol/L sodium hydroxide was added, and the tube was incubated at 65°C for 3 hours. Seven milliliters of this solution was placed into centrifuge tubes, 5 mL of 50 wt% sucrose was added, and the tube was centrifuged at 1700 × *g* for 1 hour. Polyethylene particles rose to the top of the tube and were carefully pipetted into a clean tube, suspended in distilled water, ultrasonicated for 5 minutes, and heated for 30 minutes at 80°C. Seven milliliters of this solution was placed into a fresh tube, 4 mL of isopropanol with a density of 0.96 g/cm^3 and 2 mL with density of 0.90 g/cm^3 were added, and the tube was centrifuged at 1700 × *g* for 2 hours. Finally, the band formed between the different isopropanol densities was carefully pipetted into a clean vial. Particles were tested for the presence of endotoxin using an E-TOXATE kit (E8029, Sigma-Aldrich, St. Louis, Mo). The samples were prepared from stock suspensions in the same manner as used for the cell culture experiments.

Verification of the retrieved particles as polyethylene was performed by Fourier transform infrared spectroscopy (FTIR; FTIR-8400S, Shimazu, Kyoto, Japan). The obtained particles were also observed with a scanning electron microscope (S-4700, Hitachi, Tokyo, Japan). The lengths in the long axis and the widths in the short axis of 100 particles were recorded by using image analysis software (Image-Pro Plus, version 4.0).

Preparation of Adherent Cells (Macrophages)

Peripheral blood (20 mL) was taken from patients by venipuncture using a 21-gauge needle. The blood was immediately mixed well with 2 mL of a citrate-phosphate-dextrose solution with adenine (C4431, Sigma-Aldrich) and diluted with 20 mL RPMI-1640 medium (Gibco, Invitrogen, Carlsbad, Calif) with 1% penicillin-streptomycin (P4333, Sigma-Aldrich) and 1% pyruvate (S8636, Sigma-Aldrich). Fifteen milliliters of Ficoll-Paque Plus (Amersham Biosciences, Piscataway, NJ) was added to 11 mL of the solution, and the tubes were centrifuged at 500 × *g* for 15 minutes. A white layer, which was obvious in the solution, was carefully pipetted into tubes and centrifuged at 500 × *g* for 8 minutes. The resultant pellet was washed twice with 10 mL of RPMI-1640 medium. The final pellet was incubated in two 150-mm polystyrene culture dishes (Corning Life Sciences, Acton, Mass) with RPMI-1640 medium with 3.5 ng/mL human recombinant macrophage-colony stimulating factor (M6518, Sigma-Aldrich), 10% fetus bovine serum (SH30071, HyClone, Logan, Utah), 1% penicillin-streptomycin, and 1% pyruvate at 37°C for 7 days. Cells were then washed twice with phosphate buffer solution, and those that had adhered to the dish were collected by using a 0.05% trypsin solution.

In Vitro Experiments

To ensure that the polyethylene particles were effectively phagocytosed, we suspended 1.0 mg of them with 0.5 mL of RPMI-1640 medium and ultrasonicated them for 15 minutes before

coculturing them with the adherent cells. Suspended medium was placed in 60-mm polystyrene culture dishes (Corning). Adherent cells (1.0×10^7 cells) were suspended with 0.5 mL of RPMI-1640 medium and added into the culture dish. After 3 hours, 3 mL of RPMI-1640 medium was added. The adherent cells (2.5×10^6 cells/mL) were then cultured with polyethylene particles (1.0 mg/mL) in RPMI-1640 medium at 37°C in 5% (volume/volume) CO_2 in air. Cells were incubated without polyethylene particles as a control. After 48 hours, supernatants were collected and preserved at −80°C after filtering through a 0.22-μm pore filter. Interleukin-1β, IL-6, and TNF-α were assayed with a double-antibody sandwich enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, Minn).

Assessment of Overall Results

Patient sensitivity to the polyethylene particles was defined by the severity of osteolysis in 2-dimensional images of all zones evoked per unit of polyethylene particles. That is, we used the ratio of the area of osteolysis to the volumetric polyethylene wear using the following equation:

sensitivity index
= area of osteolysis/total volumetric polyethylene wear

The relationships between the sensitivity index and the concentrations of cytokines were individually evaluated.

Statistical Analysis

Statistical analyses were done using data analysis software (StatView, version J-4.5, SAS Institute, Cary, NC). Correlations were calculated using Spearman's rank correlation coefficient. Statistical significance was considered to be at the level of $P < .05$.

Results

Radiologic Analysis of Polyethylene Wear

The mean of total volumetric wear and the mean volumetric wear rate were 949.7 mm^3 (range, 210.6-2642.7 mm^3) and 65.7 mm^3/y (range, 12.3-129.3 mm^3/y), respectively. The total volumetric wear in each patient is shown in Fig. 2A. The results from each patient correlated with statistically significant lines ($P < .001$).

Radiologic Analysis of Areas of Osteolysis

The mean total area of osteolysis was 664.6 mm^2 (range, 29.0-1252.9 mm^2); the means in the acetabulum and femur were 105.8 mm^2 (range, 0.0-296.2 mm^2) and 558.7 mm^2 (range, 29.0-1147.0 mm^2), respectively. The annual area of osteolysis for each patient is shown in Fig. 2B. Results from each patient correlated with statistically significant lines ($P < .001$-$.009$).

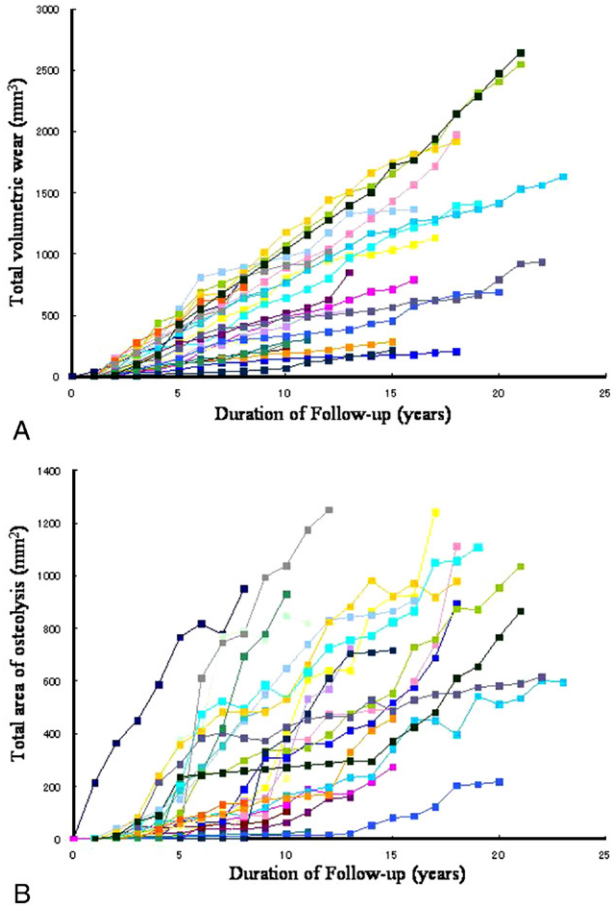

Fig. 2. Results of radiologic analysis of polyethylene wear and area of osteolysis: annual total volumetric wear (A); areas of osteolysis (B).

Reliability of the Methodology

Intraobserver reliability coefficients ranged from 0.990 to 0.998 in the measurement of polyethylene wear, and from 0.998 to 0.999 in the measurement of areas of osteolysis.

Characteristics of Polyethylene Particles

There was no evidence that polyethylene particles interfered with the ability of the assay to detect endotoxin. The FTIR spectra of isolated particles showed typical peaks at wavelengths of about 2800 and 1400 cm^{-1}, which are nearly identical to the

spectra of standard ultrahigh molecular weight polyethylene particles supplied by the manufacturer, as shown in Fig. 3A and B. The morphology of polyethylene particles was either elongated or shredlike, as shown in Fig. 3C. The mean sizes of the polyethylene particles were 1.71 μm (range, 0.20-3.66 μm) in length and 2.58 μm (range, 0.24-8.33 μm) in width.

Results of in Vitro Experiments

Fig. 3D and E are photomicrographs of human peripheral blood monocytes in culture with polyethylene particles. The mean increases in concentrations of cytokines in the supernatants, stimulated by the polyethylene particles rather than by the control, were as follows: IL-1β, 2.82 pg/mL (range,

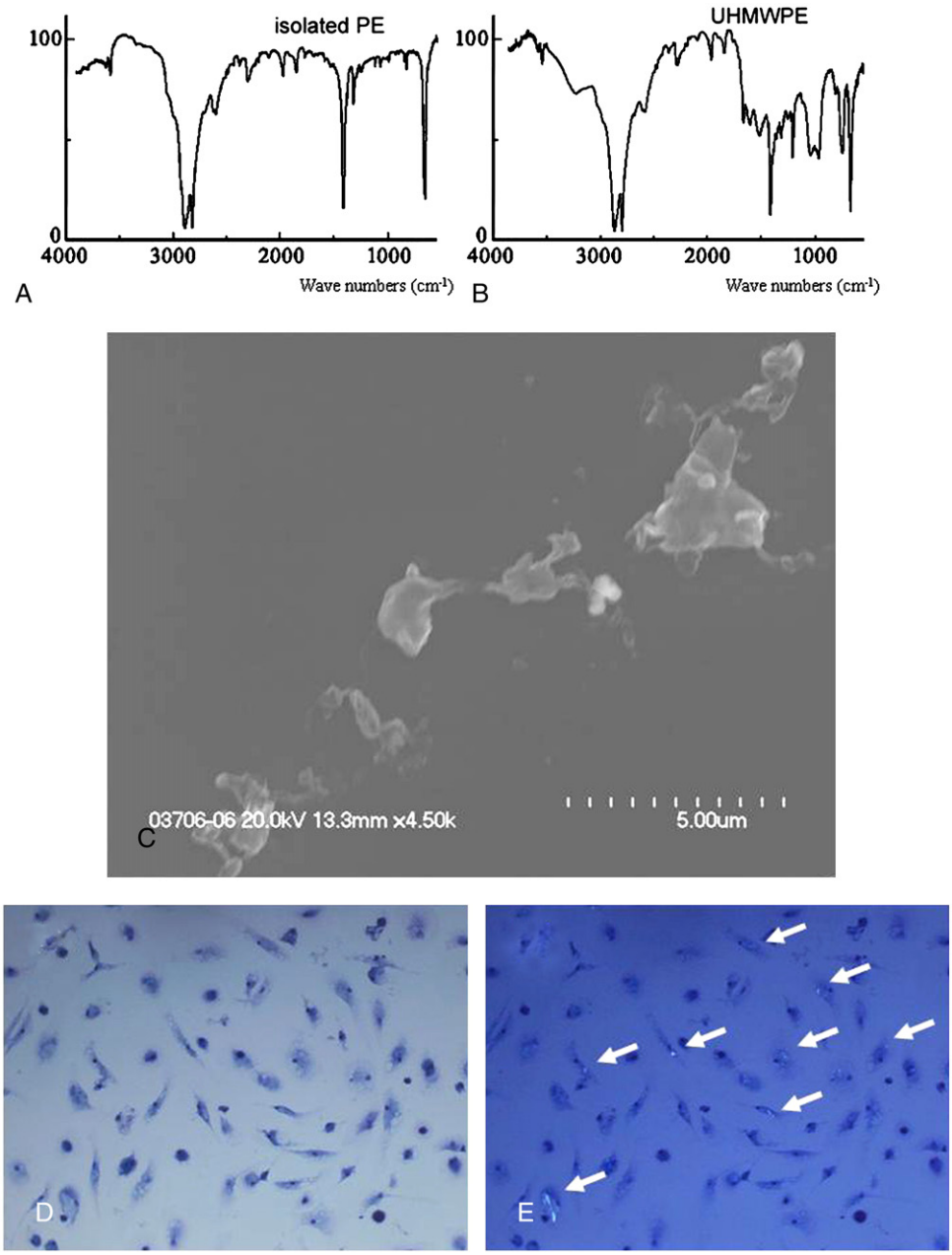

Fig. 3. Characteristics of isolated polyethylene particles. Fourier transform infrared spectrum of particles isolated from periprosthetic tissue (A). Standard ultrahigh molecular weight polyethylene particles (B). Scanning electron microscopy image of isolated polyethylene particles recorded using secondary electrons (C). Photomicrograph (×100) of human peripheral blood monocytes in culture with polyethylene particles (D). Polarized photomicrograph (×100); white arrows indicate polyethylene particles phagocytosed by macrophages (E).

0.0-9.29 pg/mL); IL-6, 294.7 pg/mL (range, 6.88-1916.2 pg/mL); TNF-α, 204.8 pg/mL (range, 6.48-799.0 pg/mL).

Overall Results

The mean calculated sensitivity index was 1.06 (range, 0.09-4.25). The log (sensitivity index) was linearly correlated with the increase in IL-6 concentrations stimulated by the polyethylene particles (R = 0.62; P = .001). However, there was no correlation with either IL-1β (R = 0.08; P = .70) or TNF-α (R = 0.30; P = .15), as shown in Fig. 4.

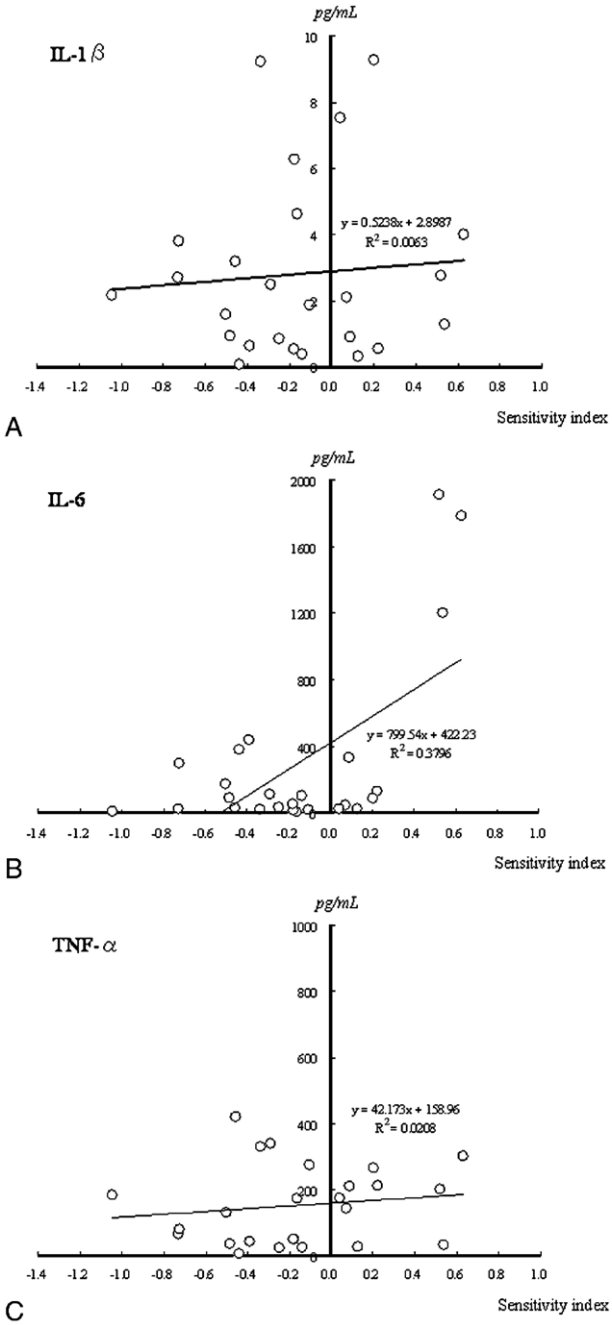

Fig. 4. Relationship between the log (sensitivity index) and the increase in concentrations of IL-1β (A), IL-6 (B), and TNF-α (C) after polyethylene particle stimulation for 48 hours.

Discussion

Because of clinical observations and experiments, the theory that periprosthetic osteolysis occurs through a biologic pathway is generally accepted [5]. However, extraordinary variations in the degree of osteolysis are sometimes encountered. In some reports [11,12] and in 1 standard textbook [13], it has been suggested that allergic hypersensitivity is related to periprosthetic loosening in patients with implanted metallic devices. Considering these circumstances, it is easy to hypothesize that sensitivity to particulate debris affects the clinical results of THA. In recent reports, although the concentration of cytokines in peripheral blood has not been different between patients with loosened implants and those with stable implants [19], human leukocyte antigen A31 phenotypes have been associated with the incidence of aseptic prosthetic loosening [20]. Also, carriage of the TNF-238 allele has been associated with an increased incidence of osteolysis [21]. These reports provide support for ethnic group or patient sensitivity to particulate debris.

To clarify this hypothesis, we measured the annual radiographic volumetric polyethylene wear and the area of osteolysis, and defined the ratio of the area of osteolysis to volumetric polyethylene wear, calculated in vivo, as the sensitivity index. Polyethylene wear progressed at a constant annual rate in each patient. However, the point at which osteolysis occurred and the speed of its development varied in each individual. In some patients, osteolysis began several years after surgery and developed with increasing speed over time. The measured area of osteolysis was also influenced by the conditions when the radiograph was taken (eg, pelvic tilting or hip rotation). However, eventually, the results for individual patients have shown statistically significant progression of osteolysis.

The cells that induce periprosthetic osteolysis are believed to be osteoclasts because they are found around loosened prostheses [22]. Many bioactive substances, including cytokines, have their own peculiar physiologic effects, and some interact with each other and act on osteoclasts in their microenvironment [23]. Interleukin-1 and TNF-α are

known as inflammatory cytokines, and 1 of their biologic activities leads to differentiation and the activation of osteoclasts, directly or indirectly, via the RANK-RANKL signaling pathway [10]. Interleukin-6 also leads to differentiation and activation of osteoclasts, although it acts directly through gp130 receptors [24] or indirectly through the RANK-RANKL signaling pathway [25]. However, no one has reported which pathway is dominant in the formation of polyethylene-induced osteolysis. Our study revealed that patient sensitivity to polyethylene particles, which in turn induces periprosthetic osteolysis, depends on the actions of IL-6 secreted by macrophages.

Some difficulties remain in establishing an experimental system for evaluating sensitivity to polyethylene particles. First, the size of polyethylene particles [26] and particle chemistry [27] have been reported to be key conditions for phagocytosis and the release of cytokines by macrophages. Polyethylene particles from periprosthetic tissue have been characterized as mostly submicron in size [28]. However, it is very difficult to obtain enough submicron particles to establish and undertake experiments. Moreover, industrial polyethylene is hydrophobic and lighter than water, so it is difficult for it to be phagocytosed by macrophages in culture medium. As a result, the polyethylene particles that we used here were relatively larger than the particles in periprosthetic tissue; as previously reported [28], they were also relatively hydrophilic but easily mixed with culture medium by ultrasonication and easily phagocytosed by macrophages, allowing observation of the reaction of macrophages. Second, the measurement method for the area of osteolysis required the use of 2-dimensional studies with plain radiographs; therefore, we cannot ignore the possibility that we underestimated the actual area of osteolysis, as in previous studies [29]. More precise noninvasive 3-dimensional assessment methods are anticipated.

In conclusion, from these experimental results, our *in vivo* sensitivity index (a measure of personal sensitivity to polyethylene particles) can be used to estimate the occurrence and development of osteolysis induced by polyethylene wear. In high-risk patients, those with higher sensitivity to particles, we can now choose joint-preserving surgery or avoid using polyethylene in favor of other materials for the bearing surface (eg, metal-on-metal THA). However, it is still unclear whether this sensitivity is innate. The possibility exists that some patients develop sensitivity and that such patients would be prone to osteolysis. We anticipate that a future, more precise prospective study will reveal the biologic threshold for sensitivity to polyethylene particles as indicated by *in vitro* experiments.

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