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ORIGINAL ARTICLE

Poly(2-methacryloyloxyethyl phosphorylcholine)-grafted highly cross-linked polyethylene liner in primary total hip replacement: one-year results of a prospective cohort study

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Abstract To control particle-induced osteolysis in total hip replacement (THR), we developed a new technique to graft poly(2-methacryloyloxyethyl phosphorylcholine) onto the surface of polyethylene liners. A prospective cohort study was conducted to investigate the clinical safety of this novel bearing surface. Between April 2007 and September 2008, we recruited a prospective consecutive series of 80 patients in five participating hospitals. These patients received a cementless THR; a 26-mm-diameter cobalt–chromium–molybdenum alloy ball and a poly(2-methacryloyloxyethyl phosphorylcholine)-grafted cross-linked polyethylene liner were used for the bearing couplings. These individuals were followed a year post-operatively. An evaluation of clinical performance was conducted through an assessment of hip joint function based on the evaluation chart authorized by the Japanese Orthopaedic Association. No patients were lost to follow-up. No adverse events were found to be correlated with the implanted liners. The average hip joint function score

For the Investigation Group into the ploy(MPC)-grafted UHMWPE liner for hip replacement.

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improved from 43.2 preoperatively to 91.7 postoperatively at 1 year. There was no implant migration nor periprosthetic osteolysis detected on radiographic analysis. On the basis of our results, we conclude that poly(2-methacryloyloxyethyl phosphorylcholine)-grafted cross-linked polyethylene liners are a safe implant option for hip replacement surgery for short-term clinical use.

Keywords Joint replacement · Hip arthroplasty · Clinical trial · Polyethylene

Introduction

Sir John Charnley read the monumental paper entitled "Arthroplasty of the hip by low-friction technique" at the spring meeting of the British Orthopaedic Association in 1961 [1]. He insisted that low friction was the key to the clinical success of artificial hip joints. In line with this thesis statement, he later used a polyethylene (PE) socket and a stainless steel ball as the bearing coupling. Most of his prostheses worked uneventfully in most patients for close to a decade; however, periprosthetic osteolysis gradually prevailed thereafter. Extensive research subsequently discovered that osteolysis was induced by wear particles from the PE sockets [2].

In most studies, one of two approaches have been adopted to reduce the generation of wear particles: (1) harden the PE or (2) replace the PE with an alternative material. Research efforts focusing on the former approach have produced several new PEs, including highly cross-linked PE (CLPE), and those concentrating on the latter have resulted in the introduction of a range of different bearing couplings, such as ceramic-on-ceramic ones. However, separate from these two approaches is a third tactic, namely, the production of an ultra-low friction surface and suppression of foreign body reactions. The researchers who are working on this approach have developed a new technique to graft poly(2-methacryloyloxyethyl phosphorylcholine) [poly(MPC)] onto the surface of PE liners. MPC is a cell membrane-inspired material synthesized industrially by Ishihara et al. [3]. Based on the results of experiments carried out by Moro et al. [4], the coefficient of dynamic friction of poly(MPC)-grafted CLPE specimens was reduced by 84 %. Moreover, poly(MPC)-grafted CLPE liners demonstrated a remarkable reduction in wear beyond 10 million cycles in hip simulator tests [5]. Although the MPC polymer coating has been applied safely to several medical devices, including stents [6] and an artificial heart [7], the effect of poly(MPC)-grafted CLPE liners on the health of their users remains an open question. Therefore, we conducted a prospective cohort study investigating the clinical safety of this novel bearing surface; the outline of this study is recorded as JapicCTI-090776. In this paper, we describe the 1-year outcome of 80 consecutive patients.

Materials and methods

Between April 2007 and September 2008, we recruited a prospective consecutive series of 80 patients in five participating hospitals. These individuals had a painful non-infectious hip disorder requiring total hip replacement (THR), which is a designation of A or B according to the Charnley classification [8]. Each institutional review board of the participating hospitals gave ethical approval, and informed consent was obtained from the participants before the study commenced. Exclusion criteria were pre-existing infection, significant comorbidities, and a previous joint-preserving procedure on the affected hip joint. Preoperative demographic data are summarized in Table 1.

All patients received the K-MAX® cementless THR (Japan Medical Materials Corp, currently Kyocera Medical Corp, Osaka, Japan) which consists of a collarless femoral stem (K-MAX® HS-6) and a low-profile porous-coated acetabular component with four peripheral fins (K-MAX®

Table 1 Pre-operative demographic data

Demographic characteristics	Values
Sex	
Male	14 (17.5)
Female	66 (82.5)
Age (years) (range 44–74; mean 61.3)	
40–49	6 (7.5)
50–59	31 (38.8)
60–69	23 (28.8)
70–75	20 (25.0)
Diagnosis	
Osteoarthritis	76 (95.0)
Osteonecrosis	4 (5.0)
Charnley category	
A	42 (52.5)
B	38 (47.5)
Side	
Right	42 (52.5)
Left	38 (47.5)
Body height (cm)	155.5 ± 6.5 (143–175)
Body weight (kg)	54.2 ± 7.5 (37–73)
Body mass index	22.4 ± 2.6 (16.5–27.0)

Data are presented as the number (of patients) with the percentage in parenthesis, except for body height, body weight, and body mass index which are presented as the mean and standard deviation (SD) with the range in parenthesis

Fig. 1 K-MAX® cementless artificial hip prostheses. **a** Cementless femoral stem (K-MAX® HS-6): a double wedge-shaped, metaphyseal filling-type stem. **b** Cementless acetabular component (K-MAX® Q5LP): a low-profile porous-coated acetabular component with four peripheral fins and three screw holes

Table 2 Laboratory tests

Tests	Items
Hematologic test	Red blood cell count
	Hemoglobin
	Hematocrit value
	White blood cell count
	Differential blood count
	Platelet count
Blood chemistry	Alanine aminotransferase
	Albumin
	Alkaline phosphatase
	Aspartate aminotransferase
	Blood creatinine
	Blood urea nitrogen
	C-reactive protein
	Electrolytes (sodium, potassium, chlorine)
	Gamma-glutamyltransferase
	Lactate dehydrogenase
	Total bilirubin
	Total cholesterol
	Total serum protein
	Uric acid
Urine	Glucose
	Protein
	Urobilinogen

Q5LP) (Fig. 1). These components are made of vanadium-free titanium alloy, and a bottom coating was applied to the porous area with apatite–wollastonite glass ceramic. For the bearing coupling, a 26-mm-diameter cobalt–chromium–molybdenum alloy ball and an poly(MPC)-grafted CLPE liner were employed. All poly(MPC)-grafted CLPE liners were manufactured from compression-molded PE sheet stock (GUR 1020 resin). The sheet stock was treated with a dose of 50 kGy gamma-ray irradiation in N_2 gas and annealed at 120 °C for 7.5 h in N_2 gas. After cooling, the liners were machined to have a 26-mm inner diameter and an elevated lip. For the poly(MPC) grafting, they were immersed in an acetone solution containing benzophenone and subsequently dried to remove the acetone. The liners were then immersed in the aqueous MPC solution, and the graft polymerization on the bearing surface was performed using ultraviolet-ray irradiation. Finally, the liners were packaged and sterilized by a dose of 25 kGy gamma-ray irradiation in N_2 gas. The surgery was performed through a posterior approach by or under the guidance of five principal investigators. Patients underwent the routine thromboprophylaxis regimen and postoperative rehabilitation program of each institution.

The patients were seen postoperatively at 3 months, 6 months, and 1 year. Orthopedic surgeons other than the operators of the index surgery followed the patients pre- and postoperatively at each institution. They measured clinical performance using the evaluation chart of hip joint function authorized by the Japanese Orthopaedic Association (JOA score) [9]. The JOA score consists of four categories, i.e., pain, range of motion, gait, and activities of daily living, with 40 points attributed to pain and 20 points to the other three categories. The sums of points from these four categories can be used as an approximate estimate for the hip function of an individual; 100 points is a perfect score and is regarded as normal.

Anteroposterior pelvic radiographs were made immediately after surgery and postoperatively at 3 weeks, 3 months, 6 months, and 1 year. Laboratory tests, including full blood counts and blood chemistry (Table 2), were performed before surgery and postoperatively at 1 and 3 weeks, 3 and 6 months, and 1 year.

Two radiologists and an orthopedic surgeon, all of whom worked at different institutions from the five participating hospitals, performed the radiographic analysis while blinded to clinical information. These experts compared radiographs taken at 3 weeks to those taken at 1 year to detect relevant findings, such as implant migration, periprosthetic osteolysis, and heterotopic ossification. The migration of the implants was defined as changes of

≥3 mm in the position of the implants [10]. Periprosthetic osteolysis was defined as a new cystic lucency localized on the endosteal surface of the bone. Heterotopic ossification was graded according to Brooker et al. [11].

All adverse events occurring during the course of this clinical trial were recorded. An adverse event was defined as any unfavorable event that occurred in the subjects during the study period. Particular attention was paid to severe adverse events, defined as: (1) those leading to death, (2) those threatening life, (3) those requiring the patient to be hospitalized or submit to an extended stay in the hospital stay, (4) those resulting in permanent or severe impairment, (5) those resulting in permanent or severe dysfunction, (6) those inducing congenital abnormalities in the offspring, and (7) those representing medically serious conditions.

Statistical methods

The paired t test was used to compare the JOA scores recorded before surgery and at 1 year after surgery.

Results

No patients were lost to follow-up at 1 year postoperatively. A total of 111 adverse events were recorded in 54 subjects, including four severe adverse events (Table 3). However, no adverse events were found to be correlated with the implanted poly(MPC)-grafted CLPE liners.

No reoperations were performed for any reasons. Dislocations occurred in two patients. The first, a 69-year-old woman (case 79), suffered a dislocation 14 days after the index surgery and was treated by manual reduction. The second, also a 69-year-old woman (case 38 in Table 3), suffered four dislocations and was treated with an abduction brace. Deep vein thrombosis occurred in three patients and was successfully treated in each case with anticoagulants.

The average of the JOA scores improved from 43.2 ± 9.7 preoperatively to 91.7 ± 9.1 postoperatively at 1 year (mean ± standard deviation) ($p < 0.01$). The change was most apparent in the category of pain (Table 4). Neither implant migration nor periprosthetic osteolysis was detected on radiographic analysis (Fig. 2). There was evidence of Brooker grade 3 heterotopic ossification in one individual without any clinical manifestations.

Laboratory tests detected abnormal changes in six patients (Table 5), including elevations in white blood cell counts and in a number of blood enzymes, such as lactase dehydrogenase. Four of these abnormal changes (cases 5, 9, 21, and 45) were the result of slight hepatic dysfunction; of these, three (cases 5, 9, 21) occurred within 1 week postsurgery and resolved spontaneously to the preoperative value without any treatments. Hence, these changes may have been drug-induced hepatic dysfunction resulting from the perioperative medication. One change (case 45) was a slight elevation of blood gamma-glutamyltransferase (36 U/L; normal <30), which was seen at the 1 year follow-up. This individual had a habit of alcohol drinking but was otherwise healthy. The other two changes (cases 39 and 54) also resolved spontaneously to the preoperative value and were not accompanied with hip symptoms.

Table 3 Severe adverse events

Case	Sex	Age (years)	Adverse events	Comments
6	Female	64	Breast neoplasm	Hospitalization for treatment
38	Female	69	Recurrent dislocation of total hip replacement	Extension of hospital stay and another hospitalization
44	Female	66	Local recurrence of rectal cancer	Hospitalization for treatment
54	Female	73	Transient myocardial ischemia	Occurred just after surgery due to blood loss during surgery. Fully recovered

Table 4 Preoperative and postoperative Japanese Orthopaedic Association score

Category	Pre-operative	Postoperative		
		3 months	6 months	1 year
Pain	11.5 ± 6.2	35.7 ± 5.3	37.9 ± 3.8	38.6 ± 3.6
Range of motion	11.6 ± 3.3	15.9 ± 2.4	16.7 ± 2.1	17.5 ± 2.3
Gait	8.8 ± 3.3	13.4 ± 4.6	16.3 ± 4.4	17.6 ± 4.3
Activities of daily living	11.4 ± 2.8	15.9 ± 3.0	17.1 ± 2.7	18.1 ± 2.5
Total	43.2 ± 9.7	80.8 ± 10.7	87.9 ± 9.2	91.7 ± 9.1

Data are presented as the mean ± SD

Discussion

The production of a novel bearing surface for an artificial joint with a new material is a challenge. Even if the results of preclinical tests are favorable, unexpected complications may occur in clinical use [12–14]. Here, we introduce a new material, i.e., a ploy(MPC), for use in an artificial hip joint.

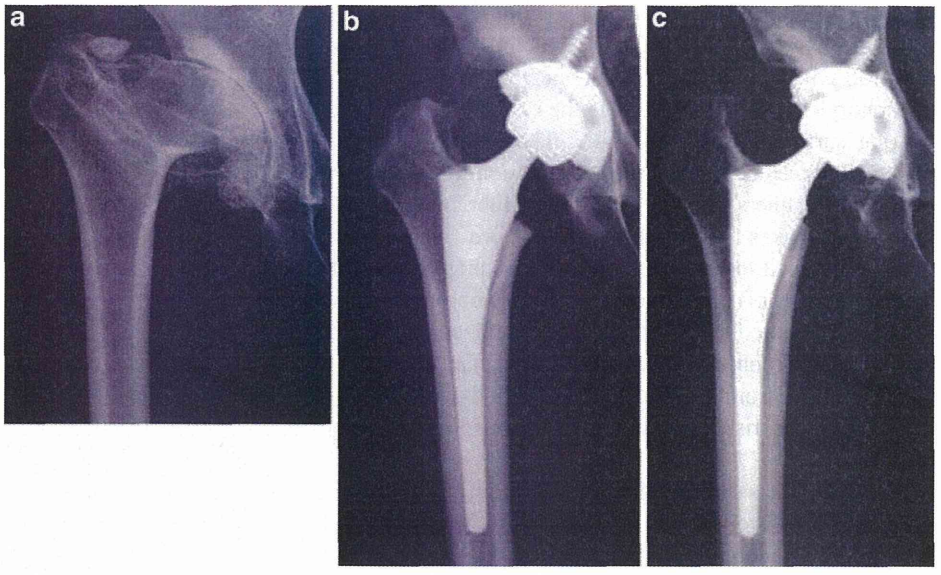

Fig. 2 Radiographs of a representative case. **a** Before surgery: radiographs show end-stage osteoarthritis of the right hip joint with severe deformity of the proximal femur. **b**, **c** Postsurgery (**b** 3 weeks postsurgery, **c** 1 year postsurgery: radiographs show no findings related to implant migration or periprosthetic osteolysis

Table 5 Patients with abnormal laboratory data

Case no.	Sex	Age (years)	Adverse events	Outcome	Presumed causes and comments
5	Female	54	Elevation of enzymes related to liver function	Normalization of enzyme levels	Drug-induced hepatic dysfunction
9	Female	62	Elevation of enzymes related to liver function	Normalization of enzyme levels	Drug-induced hepatic dysfunction
21	Female	66	Elevation of enzymes related to liver function	Normalization of enzyme levels	Drug-induced hepatic dysfunction
39	Female	57	Elevation of lactate dehydrogenase and C-reactive protein	Normalization of lactate dehydrogenase level. The value of C-reactive protein was 0.61 mg/dL at 1 year postoperatively	Preoperative value of C-reactive protein was 0.9 mg/dL without relevant findings of infection
45	Female	45	Elevation of gamma-glutamyltransferase	The value of gamma-glutamyltransferase was 36 U/L (normal <30) at 1 year postoperatively	Related to alcohol drinking
54	Female	54	Elevation of white blood cell count and C-reactive protein	Normalization of white blood cell count and C-reactive protein without specific treatment	The cause of transient abnormal data was not specified. Elevation of these values accompanied no hip symptoms

We investigated 80 consecutive patients who were implanted with poly(MPC)-grafted CLPE liners as a component of an artificial hip joint. Both the clinical assessment using the JOA score and the radiographic examinations demonstrated comparable results to other contemporary artificial hip joints [15–17].

Although more than 100 adverse events were encountered, none of which were correlated to the poly(MPC)-grafted CLPE liners. Abnormal changes in laboratory chemistry data were detected in six patients. These changes resolved spontaneously except in one individual. In this case, the elevation of the gamma-glutamyltransferase may be related to the habit of alcohol intake.

MPC is a synthesized phospholipid and is composed of a methacryloyl group and a zwitterionic phosphorylcholine group; the former is a polymerization reaction group, and the latter is a polar group. Ishihara et al. developed a new technique to graft poly(MPC) onto the PE surface using a photoinduced reaction. In this reaction, a covalent bond is first formed between the carbon atoms of the PE and a methacryloyl group of the MPC molecule. This MPC molecule then links with another MPC molecule. Through

the repetition of this polymerizing reaction, the PE surface is covered with a poly(MPC) layer having a thickness of 100–150 nm. The poly(MPC) has branch-like structures of phosphorylcholine, which change the characteristics of the bearing surface to be hydrophilic. The poly(MPC) layer presumably results in a significant reduction in the friction of the CLPE liners through a hydration–lubrication mechanism and makes the bearing surface more robust under multi-directional loadings. Moreover, phosphorylcholine is a constituent of the human cell membrane. Thus, poly(MPC)-grafted particles are not recognized as foreign bodies by macrophages and, consequently, the wear particles produced from the poly(MPC)-grafted CLPE liners have a reduced risk of resulting in serious foreign body reactions.

This study has several limitations. First, it was not a randomized controlled trial. The primary reason for not performing a randomized controlled trial was our conclusion that it would be extremely difficult to conduct such a trial for a THR, a well-established surgical procedure, in Japan. Although some individuals are willing to join a clinical trial for a new product because of its potential benefits, many often regard the process in which an implant is chosen by a chance mechanism as too experimental. Second, 80 individuals and 1 year of follow-up may be not a sufficient period of time to exclude the possibility of rare adverse reactions related to these new bearings. Thus, a long-term follow-up study (UMIN000003681) is currently underway for an extended investigation, including the measurement of PE wear.

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Research and development of metals for medical devices based on clinical needs

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TOPICAL REVIEW

Research and development of metals for medical devices based on clinical needs

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Abstract

The current research and development of metallic materials used for medicine and dentistry is reviewed. First, the general properties required of metals used in medical devices are summarized, followed by the needs for the development of $\alpha + \beta$ type Ti alloys with large elongation and β type Ti alloys with a low Young's modulus. In addition, nickel-free Ni–Ti alloys and austenitic stainless steels are described. As new topics, we review metals that are bioabsorbable and compatible with magnetic resonance imaging. Surface treatment and modification techniques to improve biofunctions and biocompatibility are categorized, and the related problems are presented at the end of this review. The metal surface may be biofunctionalized by various techniques, such as dry and wet processes. These techniques make it possible to apply metals to scaffolds in tissue engineering.

Keywords: metal, alloy, biomaterial, implant, medical device, biofunction, biocompatibility

1. Introduction

The use of metals has a long history, integral to materials science and engineering. However, metals are sometimes thought as 'unfavorable materials' for medical purposes due to the environmental and health concerns over heavy metals. With the emphasis on safety of metals for medical use, considerable effort is given to the improvement of corrosion resistance and mechanical durability. On the other hand, the technological evolution of ceramics and polymers during the last three decades has made it possible to apply these materials to medical devices; as a result, many metal devices have been replaced with those made of ceramics and polymers. In spite of this development, over 80% of implant devices are made of metals because of their strength, toughness and durability. The advantages of metals in medical devices are the following:

(a) high strength,
(b) high elasticity,
(c) high fracture toughness,
(d) a combination of high elasticity and stiffness and
(e) high electrical conductivity.

When considering the above properties, metals are generally superior to ceramics and polymers for medical devices. Therefore, it is difficult to replace metals in medical devices with ceramics or polymers.

Research and development of metals continue with the purpose of improving mechanical and surface properties, which govern their mechanical and tissue compatibility. In this paper, we review developments in the research on metallic materials used for medicine, including dentistry.

2. General properties required of metals used in medical devices

Metals are essential for orthopedic implants, bone fixators, artificial joints and external fixators since they substitute for the functions of hard tissues in orthopedics. Stents and stent grafts are placed in blood vessels for dilatation. Therefore, elasticity or plasticity for expansion and rigidity for maintaining dilatation are required in the devices. In dentistry, metals are used for restorations, orthodontic wire and dental implants.

The most important property of these biomaterials is safety. Metals implanted in tissues do not show any toxicity

Table 1. Requirements of metals for medical devices.

Required property	Target medical devices	Effect
Elongation to fracture	Spinal fixation; maxillofacial plate	Improvement of durability
Elastic modulus	Bone fixation; spinal fixation	Prevention of bone absorption by stress shielding
Superelasticity Shape memory effect	Multi-purpose	Improvement of mechanical compatibility
Wear resistance	Artificial joint	Prevention of generation of wear debris; improvement of durability
Bioderadability	Stent; artificial bone; bone fixation	Elimination of materials after healing; no need of retrieval
Bone formation Bone bonding	Stem and cup of artificial hip joint; dental implant	Fixation of devices in bone
Prevention of bone formation	Bone screw; bone nail	Prevention of assimilation
Adhesion of soft tissue	Dental implant; trans skin device; external fixation; pacemaker housing	Fixation in soft tissue; prevention of inflectional disease
Inhibition of platelet adhesion	Devices contacting blood	Prevention of thrombus
Inhibition of biofilm formation	All implant devices; treatment tools and apparatus	Prevention of infectious disease
Low magnetic susceptibility	All implant devices; treatment tools and apparatus	No artifact in MRI

without metal ion dissolution by corrosion and/or generation of debris by wear. Therefore, corrosion-resistant materials, such as stainless steel, the Co–Cr–Mo alloy, commercially pure Ti and Ti alloys, are employed. Noble-metal-based alloys, such as Au alloys and Ag alloys, are also used in dentistry.

A disadvantage of using metals as biomaterials is that they are typically artificial materials and have no biofunction. Therefore, metals require additional properties before they can be used as biomaterials. Requirements for metals in medical devices are summarized in table 1. To respond to these requirements, new alloy designs and many techniques for the surface modification of metals have been researched and even commercialized.

3. Categories of research and development

Research and development of metals for medical devices or metallic biomaterials are categorized as follows:

(1) Design of new alloys
(2) Development of working processes and heat treatments
(3) Development of new surface treatment and modification techniques
  (i) Ceramic coating and growth of surface oxide
  (ii) Immobilization of functional molecules and biomolecules
  (iii) Composite with polymers
(4) Control of surface morphology
(5) Evaluation of mechanical properties
(6) Evaluation of corrosion resistance
(7) Evaluation of safety and toxicity
(8) Evaluation of biocompatibility and biofunctions
(9) Development of *in vitro* evaluation techniques

Development of new materials is performed by (1) design of alloys, (2) development of working processes, (3) surface treatment techniques and (4) control of surface morphology. In addition, (5) the evaluation of mechanical properties is necessary because good mechanical properties are essential for metals. For medical devices, (6) the evaluation of the corrosion resistance is significant. If these properties are confirmed in new materials, (7) safety and toxicity and