Acta Med. Okayama, 2017
Vol. 71, No. 1, pp. 49–57

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Verification of Implant Surface Modification by a Novel Processing Method

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Metals have been used clinically as biomaterials, especially in the orthopaedic and dental fields. Metals used as implants wear at contact surfaces, producing metal particles and metal ions that may be harmful. Newly developed metal implants and methods of implant surface modification are currently under scrutiny. We evaluated the use of electrolytic in-process dressing (ELID) as a surface finishing method for metal implants. Metal implants processed using the ELID method (ELID group) or not processed (Non-ELID group) were inserted surgically into rabbit femurs. The rabbits were sacrificed postoperatively over a 24-week period. We assessed the concentrations of the cytokines, interleukin (IL)-1β, IL-6, and tumor necrosis factor-α, the resistance to implant pull-out, and histopathology at the implant site. There was no significant difference between the groups regarding the cytokine concentrations or implant pull-out resistance. Many particles indicating wear around the implant were noted in the Non-ELID group (n = 10) but not the ELID group (n = 13), while a fibrous membrane adhering to the every implant was noted in the ELID group. The formation of a fibrous membrane rather than metal particles in the ELID group may indicate improved biocompatibility, and it suggests that ELID may prevent corrosion in the areas of contact.

Key words: biomaterial, surface modification, metal implant, wear, metal ion

Many biomaterials have been used in medical practice, especially in orthopaedics and dentistry [1-3]. Because of their favorable dynamic properties and good workability, metals have been widely used. Metals used in implants have specific characteristics. Steinemann [4] identified vanadium as cytotoxic, and zirconium dioxide, titanium, and tantalum as not cytotoxic (*i.e.*, biocompatible). However, the wear of metals used in implants produces metal particles and metal ions [5-7]. Ferguson *et al.* [8] reported that pure titanium bars will wear when inserted into rabbit muscle. They weighed the metal in surrounding muscles and main organs, and found increasing concentrations of titanium in the muscles surrounding the implant site, as well as the lung and spleen, suggesting that pure tita-

Received December 7, 2015; accepted August 19, 2016.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

nium corrodes and dissolves.

Metal particles and metal ions have also been found to cause allergic reactions [9,10], foreign body reactions [11,12], pseudotumors [13,14], renal failure [15], pregnancy-related complications [16,17], and carcinogenesis [18-21]. In addition, osteolysis around the arthroplasty site correlates with the number and the size of wear particles [22]. It is thus important to reduce the wear of metal implants to avoid complications, and to develop new materials and methods of implant surface modification to reduce implant wear.

With regard to new methods of implant surface modification, Brama *et al.* [23] developed a method of coating titanium substrates with carbides using pulsed laser deposition to produce surfaces of titanium carbide (TiC). This process improved implant hardness, biocompatibility, and osteointegration, compared to uncoated titanium. Roy *et al.* [24] coated commercially pure titanium with a highly crystalline nano-hydroxyapatite (HA) using an inductively coupled radiofrequency plasma spray system. These investigators concluded that the HA coating reduced the time required for implant-tissue integration *in vivo*.

We have used electrolytic in-process dressing (ELID) [25] for an implant surface modification. The ELID grinding system improves surface quality while simultaneously adding surface oxide (Fig. 1). In this system, an electrode approx. 1/6th the area of the entire grinding wheel surface is set above a conducting metallic bond grinding wheel with a gap of approx. 0.3 mm. Positive potential is applied to the grinding wheel and negative potential is applied to the electrode by using a specific pulse generator (Fig. 1, upper). During machining, the potential electrolyte decomposes the conductive alkaline machining fluid, thereby generating OH− ions. At the same time, since positive potential is applied by the different circuit to the specimen, free OH− ions in the machining fluid are attracted to the work surface, resulting in an occurrence of an anodic oxidation reaction (Fig. 1, lower). The thickness and structure of the anodic oxidation film generated on the processed surface can be determined by adjusting the positive potential applied to the workpiece.

The ELID grinding system improves the implant surface by coating it with a thick oxide film. In the present study, we inserted metal implants processed using the ELID system or using conventional modification methods into rabbit femurs. We determined that biocompatibility and osteocompatibility of the implants under the influence of wear particles over the surround-

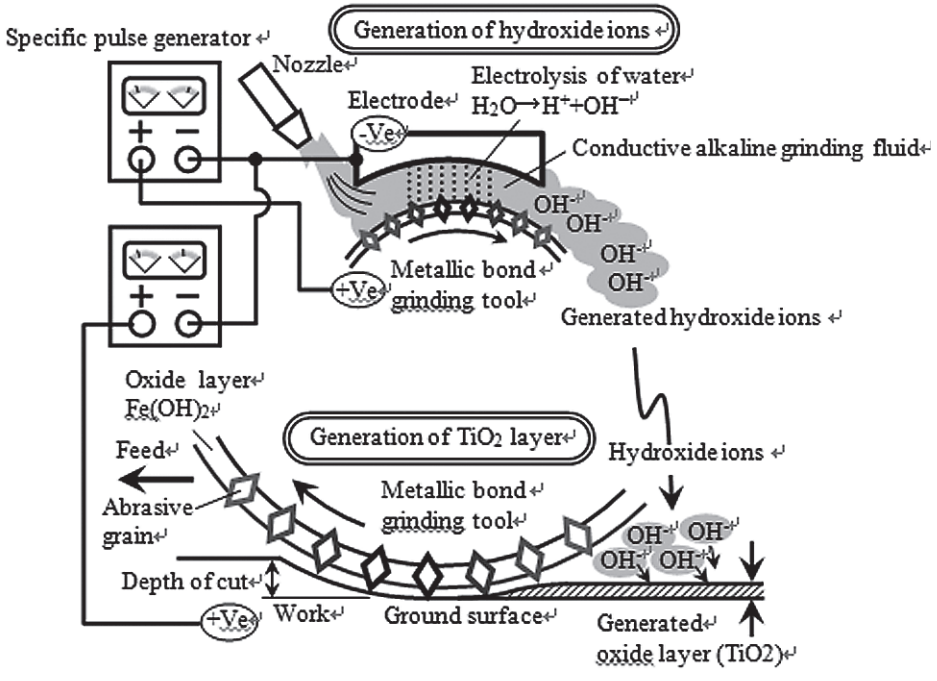


Fig. 1 The principles of a new electrical grinding system, electrolytic in-process dressing (ELID). The ELID grinding system can polish the surface and add surface oxide simultaneously.

ing tissues, and we assessed the increase of inflammatory cytokines in the blood.

Materials and Methods

The size and shape of the implant. Computed tomography (CT) of the rabbit femurs was performed three times preoperatively; based on the CT results, the most suitable implant size was determined to be 4.8 mm dia. ×30 mm long (Nakashima Medical Corp., Okayama, Japan; Fig. 2). Each implant was cylinder-shaped and hollow at one end to allow the insertion of a hook for the pull-out test. The metal composition of the implant is shown in Table 1.

Experimental animals. The Guidelines for Proper Conduct of Animal Experiments (Science Council of Japan, 2006) were observed for the entirety of this experiment. Our study protocol was approved by our institutional experimental animal care and use committee (Okayama University, ref. no. OKU-2010421). Japanese White (JW) rabbits (3 kg) were used. Implants processed using the ELID method were inserted into the femurs of 13 rabbits (ELID group), and implants processed without the ELID method were inserted into 10 rabbits (Non-ELID group). In the Control group (3 rabbits), both femurs were drilled without metal implant insertion (Fig. 3).

Ketamine hydrochloride (Ketaral®, Daiichi Sankyo Propharma, Tokyo, Japan) was injected into the rabbit

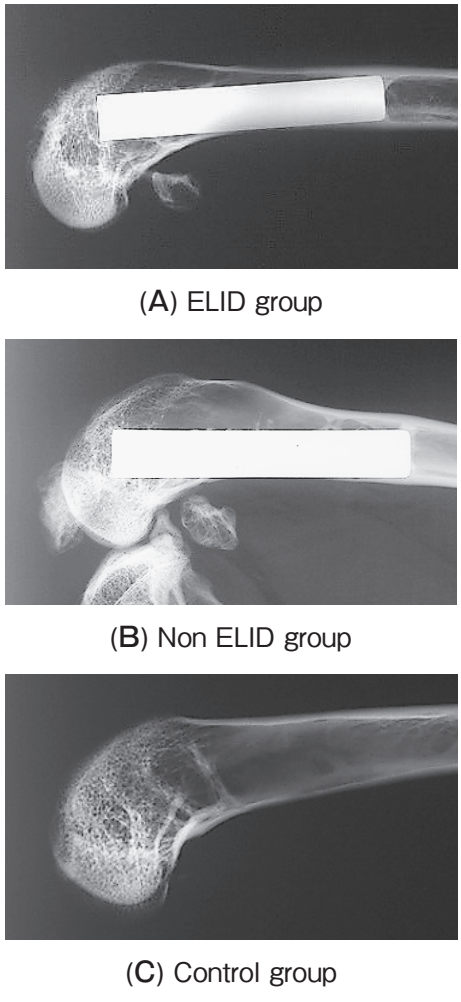


Fig. 3 X-rays of the implantation site in the (A) ELID group, (B) Non-ELID group, and (C) Control group 16 weeks after implantation. Loosening was not seen in any group.

Fig. 2 The shape of the implants. Based on CT of rabbit femurs performed three times before implantation, the most suitable implant size was 4.8 mm dia. ×30 mm. Each implant was cylinder-shaped and hollow at one end so that a hook could be inserted to perform the pull-out test.

Table 1 The composition of the metal used in our implants

C	Mn	Si	P	S	Cr	Ni	Mo	Cu	Co	N	W	Fe
0.05	0.8	0.58	0.003	0.0005	27.12	0.05	5.55	0.01	65.64	0.13	0.02	0.07

The number below each element is the composition percentage of the material used in the implants.

muscle before inhaled isoflurane (Foren®, AbbVie, Tokyo, Japan) was administered to induce general anesthesia. When the anesthesia's effect was adequate, the surfaces of both knees were shaved and sterilized with povidone-iodine. A 3-cm skin incision was made, and using the parapatellar approach, we retracted the patella laterally, exposed the femoral condyles, drilled the center of the distal femur between both condyles, and inserted the implant. After irrigation, the wound was closed. No prophylactic antibiotics were administered; no signs of infection were observed (Fig. 4).

The rabbits were observed 2, 4, 8, 16, and 24 weeks after implant insertion, and then sacrificed. Blood was obtained by cardiac puncture just before sacrifice and centrifuged at 3,000 rpm for 10 min, after which the serum was collected.

Measurement of cytokine concentration. Serum levels of interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were determined using enzyme-linked immunosorbent assay (ELISA) kits.

Pull-out test. As noted above, the implants were cylindical and hollow at one end to allow engagement of a hook for pull-out test. For this test, an implant was inserted into the femur and secured with cement, then retracted by 5 mm/min to measure the maximum load using an INSTRON device (Instron Japan, Kanagawa, Japan). The rabbits with implants that could not be removed because the implant was fully buried, the rabbits in which the hook was could not be attached, those whose implants were loose when the bone was removed to expose the surface, and those with fractured femurs were excluded from the subsequent analyses.

Pathologic evaluation. Decalcified femur specimens (80-μm thick) were prepared for both the ELID and Non-ELID groups. The specimens were cut through the middle portion of the implant and 5 mm from both ends of the implant along the minor axis (Fig. 5), and through the middle portion along the major axis. These were observed using an optical microscope (OLYMPUS BX-50, Olympus, Tokyo,

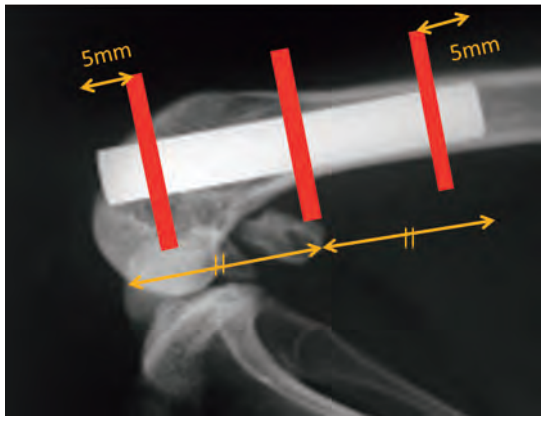


Fig. 5 The points along the length of specimen at which specimen was cut. The specimens were cut in the middle portion of implants and 5 mm on either end of the implants across the minor axis.

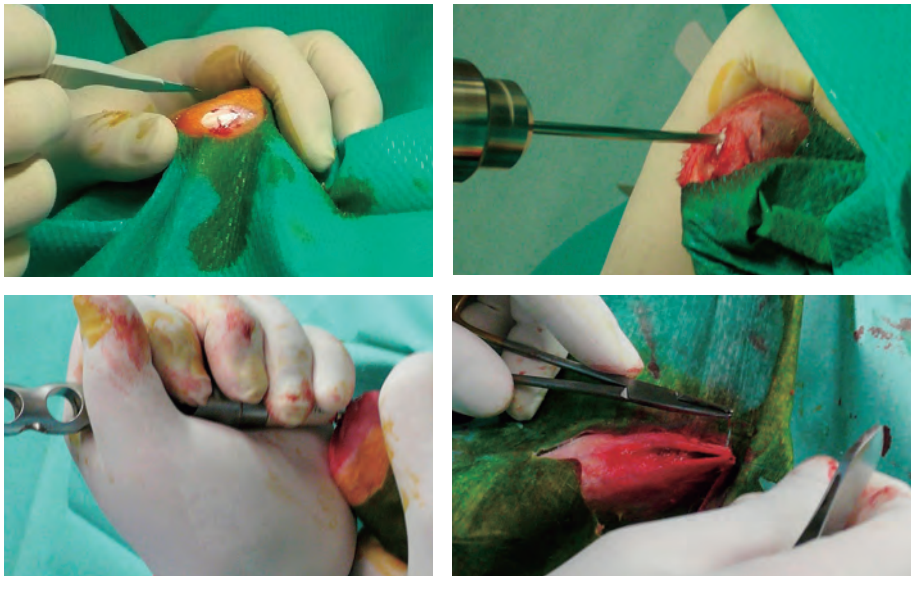


Fig. 4 The steps of the implant operation. We used the parapatellar approach, exposed the femoral condyles, drilled into the center of the distal femur between both condyles, and inserted implants that underwent the ELID process. Wound closure was performed after irrigation.

Japan), a confocal laser scanning microscope (Carl Zeiss LSM510, Munich, Germany), and fluorescence microscope (Olympus BX-50).

Statistical analysis. Graphical data are presented as the mean value ± standard deviation. Parametric data were analyzed by an analysis of variance (ANOVA) and Tukey's test using SPSS version 19.0 software (IBM, New York, NY, USA). When differences between groups were significant, the Mann-Whitney *U*-test was performed with Holm's correction. If the data were not parametric, then Student-Newman-Keuls test was performed. A p-value < 0.05 was considered significant.

Results

Measurement of cytokine concentration. There was no significant difference in the IL-1β or IL-6 levels between the ELID group (n = 13) and Non-ELID group (n = 10) (Fig. 6); a significantly higher TNF-α level was observed in the Non-ELID group at 8 weeks.

Pull-out test results. In both groups, resistance to the pull-out of the implants increased up until 8 weeks, then decreased in both groups (Fig. 7). No significant difference in resisance between the groups was observed at any time.

Pathologic evaluation. In sections through the minor axis in the center of the implants, many metal particles surrounded all of the implants in the Non-ELID group, whereas fibrous tissue and only a few metal particles surrounded the implants in the ELID group (Fig. 8). This membranous and fibrous formation was shown along the long axis of all the implants in the ELID group. Moreover, the mononuclear cells infiltration and recruitment were observed in the surrounding tissue and giant cell formation in the Non-ELID implants, whereas there were little mononuclear cell

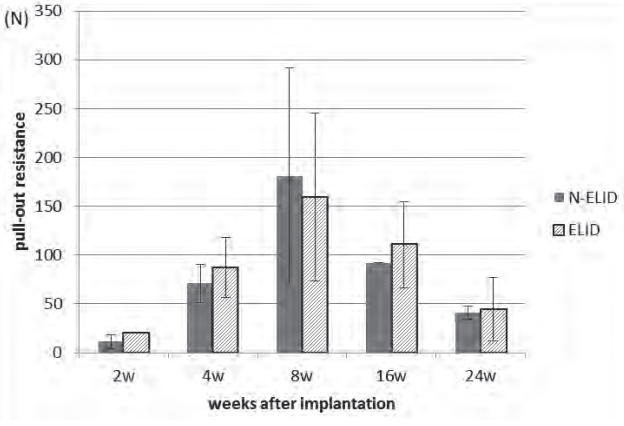
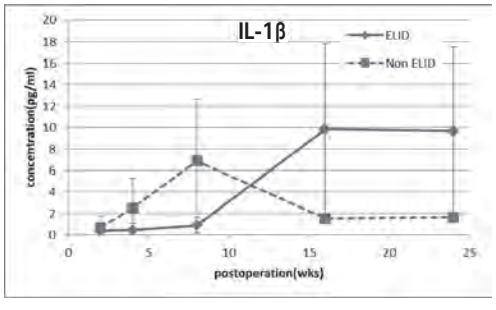
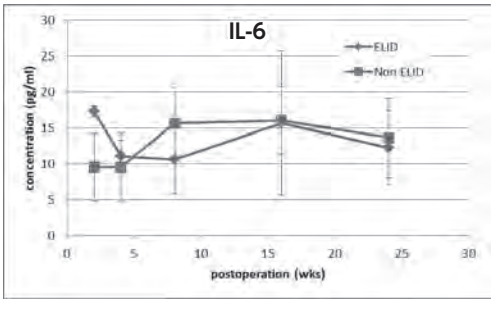


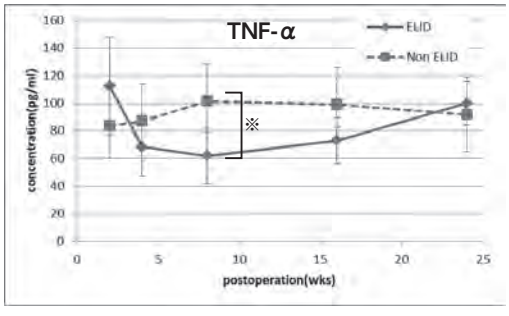
Fig. 7 The pull-out resistance. In both groups, the pull-out resistance increased up to 8 weeks, and decreased thereafter.



(A) IL-1β

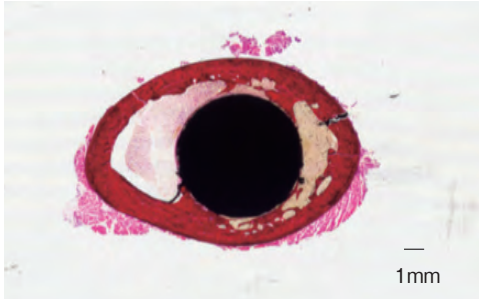


(B) IL-6

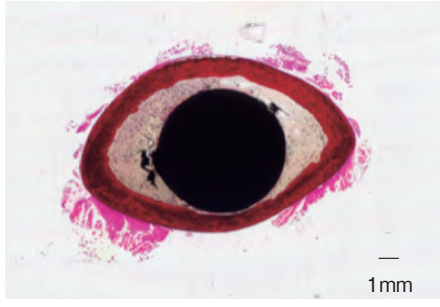


(C) TNF-α

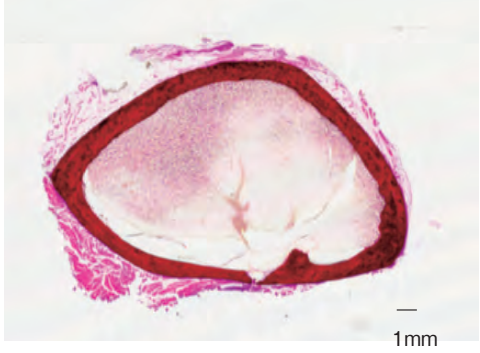
Fig. 6 The serum concentration of IL-1β, IL-6, and TNF-α cytokines. A significant difference in only TNF-α seen at 8 weeks (※: $p < 0.01$).



(A) ELID group

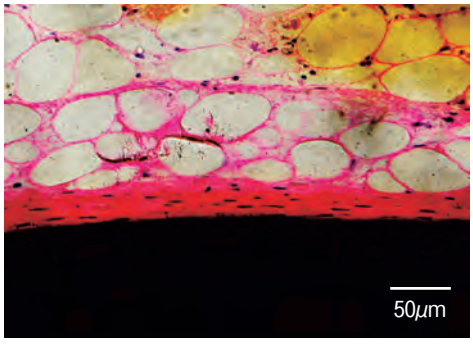


(B) Non ELID group

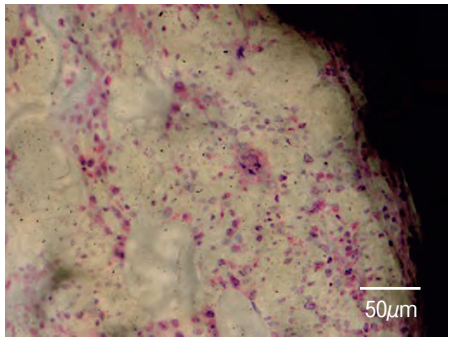


(C) Control group

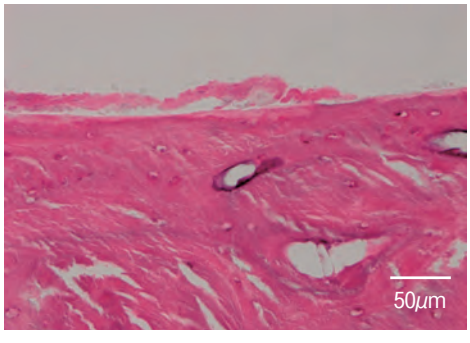
Fig. 8 The minor axis of the implant site. Metal particles surrounding the implant are abundant in Non-ELID group specimens and much less in ELID group specimens. No metal particles were seen in the Control group specimens, which implies that processing of the specimens did not contribute to the accumulation of metallic particles.



(A) ELID group



(B) Non ELID group



(C) Control group

Fig. 9 High magnification of the implant cross-sections through the minor axis. (A) ELID group, (B) Non-ELID group, (C) Control group. The metal particles surround a Non-ELID group implant are clearly visible.

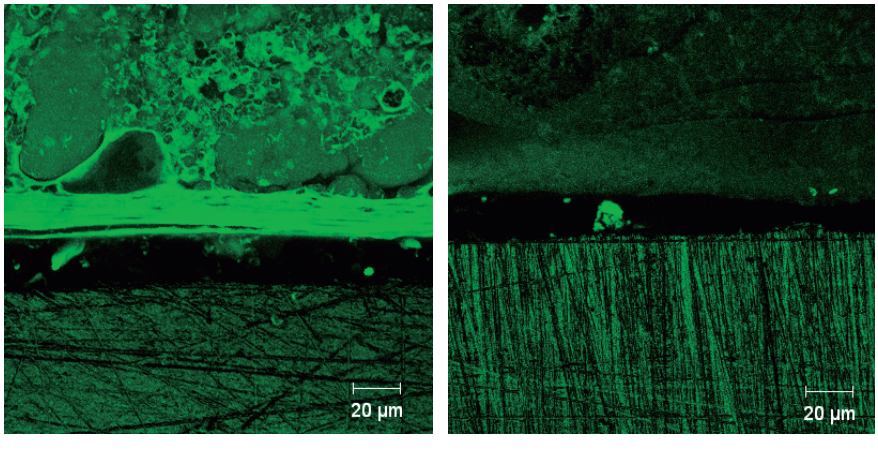
infiltration at the smooth fibrous membrane at the ELID implants (Fig. 9)

No metal particles were detected in Control group, which meant that the cutting edge of the drill was not the source of these particles. Confocal laser scanning microscopy showed a membrane of uniform thickness around the implants in the ELID group but no membrane around the Non-ELID implants (Fig. 10). Fluorescence microscopy revealed the membrane in the ELID implants but not in the Non-ELID implants (Fig. 11).

Discussion

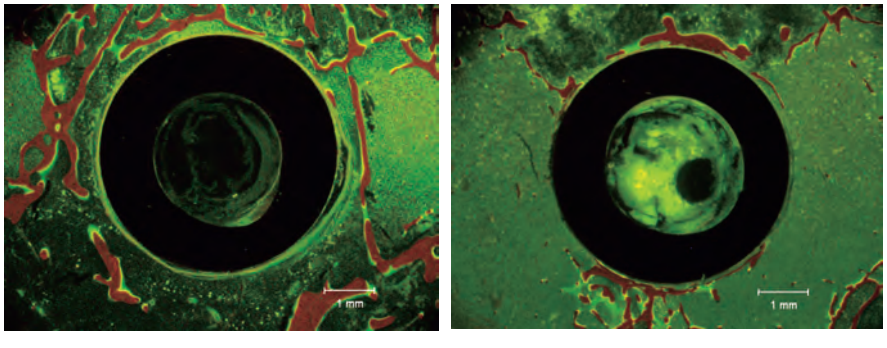
Metal implants are used clinically, but they present problems related to the release of both particles and ions. Procedures to reduce wear on implants include the use of new metal materials and surface modifications of the metal. As for the development of new metal materials, Lin *et al.* [26] reported that formation of new bone around Ti-7.5 Mo alloy implants was superior to that around Ti-6Al-4V alloy implants. According to a study by Miura *et al.* [27], a Ti-Nb-Sn alloy was similar to human bone in elasticity, and equivalent to a Ti-6Al-4V alloy in biocompatibility. Niinomi *et al.* [28] reported that compared to a Ti-6Al-4V alloy, a Ti-29Nb-13Ta-4.6Zr alloy had temperature-dependent fatigue properties and a much smaller Young's modulus. Although these new materials are more biocompatible, the clinical application of these materials awaits further translational research.

There are many surface modification processing techniques. We introduced the ELID method of coating a metal surface with a stable oxide film. In conventional surface processing after the metal is polished, a special device or specific etchant is needed, whereas in the ELID system, the surface modification and the polishing of any metal are carried out simultaneously.



(A) ELID group (B) Non ELID group

Fig. 10 Confocal laser scanning microscopy image. (**A**) ELID implant, (**B**) Non-ELID implant . A membrane surrounds the ELID implant.



(A) ELID group (B) Non ELID group

Fig. 11 Fluorescence microscopy image. (**A**) ELID implant, (**B**) Non-ELID group A membrane encircles the ELID group implant but not the Non-ELID group implant.

Moreover, the ELID system can be applied to any type of metal materials.

In this study, the difference in TNF-α level between the ELID and Non-ELID groups was significant only at 8 weeks; the IL-1β and IL-6 levels did not significantly differ between the groups at any time point. IL-1, IL-6, and TNF-α are involved in metal dissolution. Akatsu *et al.* [29] mentioned that IL-1-induced osteoclast recruitment requires a direct interaction between osteoclast progenitors and osteoblastic cells. Our present findings demonstrated that the IL-1β level tended to be higher at 16 and 24 weeks in the ELID groups. This elevation might result in the stimulation of osteoblastic cells, leading to osteoconduction. Tamura *et al.* [30] reported that increased levels of circulating or locally produced soluble IL-6 increases osteoclastic bone resorption. Merkel *et al.* [31] concluded that TNF-α mediates osteolysis. In a study similar to ours, Castellani *et al.* [32] inserted rods made of a magnesium alloy (Mg-Y-Nd-HRE) and titanium alloy (Ti-6Al-7Nb) into rabbit femurs and measured the serum IL-6 levels at 4, 12, and 24 weeks. They found little difference in the cytokine levels at any time point, indicating that normal conditions had been maintained and homeostasis had not been adversely affected.

In the present study, the pull-out test results for the ELID-treated implants and the conventionally treated implants were similar. Resistance to pull-out increased until 8 weeks. Our measurement of the femoral shaft isthmus, canal, and neck using Photoshop Creative Suite 6 software (Adobe Systems, San Jose, CA, USA) detected an increase in the length of the isthmus over time, and then the formation of an interspace between the cortex bone and implant, suggesting that surface modification by the ELID system failed to improve osteointegration between the cancellous bone and metal implant.

Machida [33] compared the pull-out resistance of Ti-6Al-4V and Ti-15Al-4Cr-4Co alloy implants in rabbits before and after blast processing, and no significant difference in pull-out resistance was revealed between the alloy groups, but greater osteointegration was observed in the blasted implants. Kim *et al.* [34] used pull-out tests to investigate the mechanical effects of treatment with hydrogen peroxide solution containing tantalum chloride on titanium fiber mesh implanted into the femurs of adult beagles. They found that the bone bonding strength of the treated implants was higher than that of the untreated implants at 3 and 5 weeks after implantation but almost equal at 8 weeks after implantation. It thus remains unclear whether a surface modification of the metal promotes osteoconduction only at the early stage after implantation.

In the present study's Non-ELID group, we noted tissue metallosis of the implant bed and many macrophages containing metal wear particles. In the ELID group, a membrane surrounding the implant was seen on confocal laser scanning microscopy and a fibrous membrane surrounding the implant was observed on fluorescence microscopy. This membrane indicates that the surface processing of the implant increases the biocompatibility and reduces the amount of foreign body reaction.

Facca *et al.* [35] found no tissue degeneration, neutrophil infiltration, or macrophage phagocytosis of HA-CNT (carbon nanotubes) around implants made of Ti-6Al-4V metal alloy coated with HA-CNT in their transmission electron microscopy examination. Pieske *et al.* [36] prospectively compared pin-track complications of titanium alloy pins versus stainless steel pins in external fixation at the wrist. The rates of pin-loosening for the stainless steel and titanium alloy pins were 10% and 5%, respectively. The lower rate of complications suggests better biocompatibility.

To improve biocompatibility, it is important to avoid metallosis, and thus ELID processing of metal implants is preferable.

We investigated whether the ELID processing of metal implants affected cytokine concentrations, pull-out resistance, and histopathology at the implant site. The differences in cytokine concentrations and pull-out resistance were almost insignificant. However, a fibrous membrane surrounded the metal implants and almost no metallosis was seen after the implants were surface-modified by ELID.

In conclusion, the new surface-modification process ELID is a useful option to prevent complications associated with implantation of metal devices.

Acknowledgments. We thank Mr. Yoshitaka Tsunashima, Mr. Rikito Ishii, Ms. Aki Yoshida and Ms. Reina Tanaka for their assistance in performing the experiments and preparation of microscope slides.

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