Implant Applications of Highly Corrosion-Resistant Ti-15Zr-4Nb-4Ta Alloy

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The release of metal ions from the Ti-15Zr-4Nb-4Ta alloy in pseudo body fluids was compared with those from Ti-6Al-4V and vanadium-free Ti-6Al-7Nb alloys widely used as implantable titanium alloys throughout the world, in order to choose an optimum acceleration solution for immersion testing. Bone plates, artificial hip joints of the cementless type and artificial tooth implants were experimentally fabricated using the Ti-15Zr-4Nb-4Ta alloy. The quantities of titanium ions released from the titanium alloys into phosphate-buffered saline, α -medium and fetal bovine serum were very small, and much lower than those released into 1.2 mass% L-cysteine, 0.05 mass% HCl and 1 mass% lactic acid solutions with lower pH values than the phosphate-buffered saline and α -medium. It was suggested that 1 mass% lactic acid solution was promising as an acceleration solution for immersion test. The quantities of titanium ions released from the Ti-15Zr-4Nb-4Ta alloy into fetal bovine serum, 1.2 mass% L-cysteine, 0.05 mass% HCl and 1 mass% lactic acid solutions were approximately 30% of those of titanium ions released from the Ti-6Al-4V alloy. The total quantity of zirconium, niobium and tantalum ions released from the Ti-15Zr-4Nb-4Ta alloy was much smaller than that of elements released from the Ti-6Al-4V and Ti-6Al-7Nb alloys. Bone plates, artificial hip joints and artificial tooth implants were successfully fabricated with the Ti-15Zr-4Nb-4Ta alloy using conventional manufacturing processes. The Ti-15Zr-4Nb-4Ta alloy with its excellent corrosion resistance is expected to become the preferential titanium alloy for implant applications in the future.

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1. Introduction

The population over 65 years old is increasing every year in Japan, and the use of implants is also increasing markedly (Fig. 1). The use of artificial joints, artificial bone plates, stents, and artificial bone has been markedly increasing since 1995. In Japan, implant devices imported from the US or Europe are used more often than domestic implants. Therefore, encouraging Japan's domestic industry to manufacture new implants and conforming these implants to the configuration of Japanese bone is an important issue. Implants require both biomedical safety and mechanical compatibility. It is also essential that implant materials do not exhibit any cytotoxicity, genetic toxicity or carcinogenicity. Regarding mechanical compatibility, it is necessary that the mechanical

properties and corrosion resistance do not degrade over prolonged use.

Unalloyed titanium and Ti-6Al-4V alloy are increasingly used in implants and other medical applications because they have higher mechanical strength and more excellent corrosion resistance than stainless steels and Co-Cr-Mo alloy. The quantity of titanium alloy used in domestic implants in Japan has been increasing in the past years, and was about 4 tons in 2000.

The release of metal ions from titanium implants in humans¹⁻⁸⁾ and animals⁹⁻¹⁵⁾ has been reported. The toxic effect of metal ions released from prosthetic implants has been reviewed.¹⁾ The tissues adjacent to the prosthesis in nine hips with failed Ti-6Al-4V alloy total hip replacements have been histologically examined.²⁾ The giant-cell reaction appeared around the polyethylene debris and wear particles of the cement in the failed Ti-6Al-4V alloy total hip replacements, and it increases with increasing titanium, aluminum and vanadium concentrations in the dry tissue. The mean titanium concentration in serum for patients with a loose total hip replacement made of Ti-6Al-4V alloy (8.1 ng/mL) is slightly higher than that for patients with a normally functioning primary cementless total hip replacement (4.1 ng/mL).³⁾ The slow accumulation of aluminum and vanadium ions released into the soft tissue surrounding the prosthesis has been reported.⁵⁾ On the release of metal ions from titanium materials into pseudo-body fluid, considerable research has also been conducted.¹⁶⁻²¹⁾ In particular, in order to reduce the harmful release of metal ions such as vanadium, the effects of various surface treatments on the dissolution of implant materials have been examined intensively.

Vanadium is considered to be an essential element in the body, but is classified in the toxic group at excess levels;¹⁷⁾

Fig. 1 Total expenditure for various implants in Japan.

Fig. 2 Relationship between log polarization resistance and cytocompatibility with fibroblast (a) and osteoblast (b) cells.

aluminum is classified in the capsule (scar tissue) group. Titanium, zirconium, niobium and tantalum exhibit excellent biocompatibility, and are in the loose connective vascularized (vital) group as regards tissue reaction.²²⁾ It has been reported that of the 70 metals in the periodic table, only zirconium and titanium support osteoblast growth and osteointegration, as summarized in Fig. 2.²³⁾ As the relative growth ratio of fibroblast or osteoblast cells shown on the Y-axis decreases from 1, the cytotoxic effect of metal increases. Titanium, zirconium, niobium and tantalum on the right-hand side of the X-axis have considerably superior corrosion resistance. The effects of various metals on cell viability have been reported using metallic particles.^{24–26)} The colony formation ratio of the V79 cells derived from the lung tissue of a Chinese hamster and the growth ratios of the murine fibroblast L929 and murine osteoblastic MC3T3-E1 cells relative to the control cells sharply decreased when the vanadium concentration in the medium was increased to 0.2 mg/L, and it became zero at approximately 0.5 mg/L. Since the quantities of the metal ions released into the medium were small (<0.3 mg/L) for titanium, zirconium, tantalum and niobium particle extractions, the relative growth ratios of the L929 and MC3T3-E1 cells were equal to 1 (non-cytotoxic).²⁶⁾

The vanadium-free Ti–6Al–7Nb alloy is specified in the International Standard Organization (ISO) 5832-11 standard as an $\alpha + \beta$ type. The near- β type Ti–13Nb–13Zr alloy is specified in the American Society for Testing and Materials (ASTM) F 1713 standard. The β type Ti–12Mo–6Zr–2Fe alloy, which has a slightly lower Young's modulus than the $\alpha + \beta$ type alloy, is specified in the ASTM F 1813 standard. Unalloyed tantalum for surgical applications is specified in the ISO 13782 standard.

Our research group has reported on the effects of zirconium, niobium, tantalum, tin and palladium with regard to their mechanical property and biocompatibility with cultured

Fig. 3 Comparison between effect of V ions released from Ti–6Al–4V alloy wear powder generated with an apatite ceramic pin and effect of V ions obtained in the case of medium extraction using high-purity V particles on the relative growth ratios of MC3T3-E1 cells.

cells, and on the corrosion resistance of alloys using anodic polarization tests in a pseudo-body fluid.^{27–38)} The anodic polarization property of titanium alloy was improved when zirconium, niobium, tantalum and palladium were added because the resultant ZrO_2 , Nb_2O_5 , Ta_2O_5 and PdO strengthened the TiO_2 passive film that formed on the titanium alloy. The titanium alloy disk was worn with an apatite ceramic pin in Eagle's medium, and the wear powder was sterilized in ethanol and added to the culture medium.³⁷⁾ The growth ratios of the L929 or MC3T3-E1 cells with the Ti–6Al–4V alloy wear powder relative to the control cells decreased lower than those that with the Ti–15Zr–4Nb–4Ta alloy wear powder. The concentration of vanadium released from the wear powder into the medium increased with increasing amounts of wear powder. This effect on the relative growth ratios of MC3T3-E1 cells approximately agreed with the results estimated from medium extraction using high-purity vanadium particles, as shown in Fig. 3. For the Ti–15Zr–4Nb–4Ta wear powder, the maximum titanium concentration released from the wear powder roughly agreed with the results obtained using high-purity titanium particles. In contrast, for zirconium, niobium and tantalum, the maximum metal concentrations released from the wear powders were much lower than those obtained with high-purity metal particles. The effect of friction on the anodic polarization properties of the metallic biomaterials in pseudo-body fluids has been investigated.³⁸⁾ The Ti–15Zr–4Nb–4Ta alloy exhibited excellent corrosion resistance under friction.

In this study we compare the release of metallic elements among Ti–6Al–4V, vanadium-free Ti–6Al–7Nb and Ti–15Zr–4Nb–4Ta alloys in pseudo-body fluids. In particular, the influence of an amino acid in 1.2 mass% L-cysteine, 1 mass% lactic acid and 0.05 mass% HCl solutions on titanium ion release was examined in order to choose an optimum acceleration solution for immersion testing. Moreover, bone plates, artificial hip joints and artificial tooth implants were

Table 1 Chemical composition (mass%) of materials used.

Titanium alloy	Zr	Nb	Ta	Pd	Al	V	Fe	O	N	H	C	Ti
Ti-6Al-4V ELI	—	—	—	—	6.24	4.19	0.179	0.174	0.0032	—	0.007	Bal.
Ti-6Al-7Nb	—	6.55	0.01	—	5.97	—	0.22	0.18	0.01	0.001	0.01	Bal.
Ti-15Zr-4Nb-4Ta	14.83	3.97	4.01	0.16	—	—	0.04	0.22	0.05	0.0057	0.01	Bal.

Fig. 4 Relationship between minimum values for ultimate tensile strength and total elongation specified in ISO and JIS standard.

experimentally fabricated using the Ti-15Zr-4Nb-4Ta alloy to examine whether this new titanium alloy could be adopted for the conventional manufacture of Ti-6Al-4V and Ti-6Al-2Nb-1Ta alloys.

2. Experimental Method

2.1 Alloy specimens

The titanium alloys currently specified in the Japanese Industrial Standard (JIS) T 7401, namely $\alpha + \beta$ type Ti-6Al-7Nb, and Ti-15Zr-4Nb-4Ta containing 0.2%Pd, 0.2%O and 0.05%N, were melted by vacuum-arc melting. After β forging (at 1050°C for 4 h) and $\alpha - \beta$ (starting temperature: 750°C) forging, the Ti-15Zr-4Nb-4Ta and Ti-6Al-4V alloys were annealed for 2 h at 700°C and then cooled in air. The Ti-6Al-7Nb alloy was annealed for 2 h at 740°C. The chemical compositions of these titanium alloys are shown in Table 1. The beta transus and density of the Ti-15Zr-4Nb-4Ta alloy were 795°C and 4.98 Mg/m³ (g/cm³), respectively. The minimum values of ultimate tensile strength and total elongation for the titanium alloys specified in the ISO 5832 standard are summarized in Fig. 4. The minimum values of the mechanical properties of the titanium alloys originally developed for medical use in Japan and specified in the JIS 7401 standard are also compared in Fig. 4.

2.2 Static immersion test

The static immersion test was performed in accordance with the currently specified JIS T 0304 standard. Five plate specimens, each 20 mm × 40 mm × 1 mm thick, were cut from each of the Ti-6Al-4V, Ti-6Al-7Nb and Ti-15Zr-4Nb-4Ta alloy specimens. Static immersion tests were conducted in phosphate-buffered saline [PBS(-) containing per 1 L NaCl: 8 g, KCl: 0.2 g, Na₂HPO₄: 1.15 g, KH₂PO₄: 0.2 g, pH = 7.2; Nissui], α -medium (α -modified Eagle's medium, powder, pH = 8.4: ICN Biomedicals Inc., U.S.A.) and fetal bovine serum (pH = 7.1), 1.2 mass% L-cysteine (pH = 2.1),

1 mass% lactic acid (pH = 2.6) and 0.05 mass% HCl (pH = 2.0) solutions at 37°C. The 1.2 mass% L-cysteine solution was prepared from L-cysteine hydrochloride monohydrate. The 0.05 mass% HCl solution was prepared from ultrahigh-purity hydrochloric acid concentrate (TAMAPURE-AA-10, Tama Chemicals Co., Ltd.). The α -medium solution contained 10 vol% fetal bovine serum and 7.5% NaHCO₃ solution (1 vol%).²⁴⁾

The plate specimens were surface-finished with waterproof emery paper up to 1000 grit under running water and then ultrasonically cleaned. These specimens were placed in polypropylene bottles and separately sterilized in an autoclave for 30 min at 121°C. The polypropylene bottles used for the immersion tests were carefully cleaned with 5 vol% concentrated HNO₃ solution and ultrapure water (18.3 M Ω) to remove impurities, and thereafter sterilized in an autoclave. Phosphate-buffered saline solution was also sterilized in an autoclave. The other solutions, except for the 0.05 mass% HCl solution, were sterilized with a 0.2 μ m membrane filter. Then 50 mL of the solutions was poured into the polypropylene bottles containing the plate specimens. The bottle lids, except for those containing the α -medium, were tightly sealed to maintain aseptic conditions. Bottles containing the α -medium were not tightly sealed to adjust pH. All the bottles were kept inside an incubator in a 95% air-5% CO₂ atmosphere for 7 d at 37°C.

The concentrations of titanium, aluminum, vanadium, zirconium, niobium and tantalum were determined using inductively coupled plasma-mass spectrometry (ICP-MS).³⁷⁾ The isotopic mass numbers used were as follow: Ti:49, Al:27, V:51, Zr:90, Nb:93 and Ta:181 so as to minimize the influence of the matrix. Single-element standard solutions (SPEX CertiPrep, Inc., 1000 μ g/mL) were diluted for use as the titanium, aluminum, vanadium, zirconium, niobium and tantalum standard solutions. The working curves were established in concentrations of 5 points and above. Inductively coupled plasma-mass spectrometry measurement was performed in a clean room (class 10000) and the measurement solutions were prepared in a clean bench (class 100). The analytical detection limits for the metal elements under these conditions were all below 0.05 ng/g. The solutions for analysis were stored in Falcon centrifugal containers cleaned with 5 vol% concentrated HNO₃ solution and ultrapure water.

A solution without a metallic specimen was kept under similar conditions and used for the blank test. The quantity of each metal ion (μ g/cm²) released from the titanium alloys was estimated using the following formula: (amount of solution: 50 mL) × [(metal concentration in each test solution) - (mean metal concentration in blank test with three bottles)] / (surface area of specimen). The average and standard deviation values of the quantities of released metallic ions were calculated for five bottles.

Table 2 Comparison of quantity ($\mu\text{g}/\text{cm}^2$) of various metal ions released from Ti alloys.

Solution	Ti-6Al-4V ELI			Ti-6Al-7Nb			Ti-15Zr-4Nb-4Ta			
	Ti	Al	V	Ti	Al	Nb	Ti	Zr	Nb	Ta
PBS(-)	—	—	—	—	—	—	—	—	—	—
α -Medium	—	—	—	—	—	—	—	—	—	—
Fetal bovine serum	0.02 ± 0.007	—	—	0.02 ± 0.004	—	0.0003 ± 0.0001	0.006 ± 0.001	—	—	—
1.2 mass% Cysteine	1.07 ± 0.02	0.09 ± 0.001	0.03 ± 0.001	0.77 ± 0.01	0.068 ± 0.01	0.015 ± 0.0007	0.26 ± 0.007	0.008 ± 0.004	—	—
0.05 mass% HCl	1.59 ± 0.01	0.12 ± 0.02	0.06 ± 0.001	1.12 ± 0.02	0.09 ± 0.002	0.018 ± 0.001	0.38 ± 0.03	—	0.02 ± 0.001	—
1 mass% Lactic acid	1.77 ± 0.05	0.12 ± 0.02	0.06 ± 0.002	1.77 ± 0.05	0.14 ± 0.01	0.13 ± 0.005	0.54 ± 0.01	0.044 ± 0.01	0.019 ± 0.001	0.011 ± 0.001

—: Not Detected

3. Results and Discussion

3.1 Metal release

The quantities of each metal ion ($\mu\text{g}/\text{cm}^2$) released from the Ti-6Al-4V, vanadium-free Ti-6Al-7Nb and Ti-15Zr-4Nb-4Ta alloys were obtained by immersion test in pseudo body fluids, and are summarized in Table 2. It was observed that the quantities of the titanium ion and each element released from these three titanium alloys changed depending on the element added to the titanium alloy and the composition of the immersion test solution. The quantities of the titanium ions released into the PBS(-), α -medium and fetal bovine serum were very small and much lower than those released into the 1.2 mass% L-cysteine, 0.05 mass% HCl and 1 mass% lactic acid solutions with lower pH levels than the medium solution. The quantity of the metal ions released from the titanium alloy became considerably larger in the 1.2 mass% L-cysteine solution with an amino acid. In particular, the quantities of metal ions released into the 1 mass% lactic acid solution followed by the 0.05% HCl solution were the highest in the 1.2 mass% L-cysteine, 0.05 mass% HCl and 1 mass% lactic acid solutions. The quantity of titanium ions released from the polished Ti-6Al-4V alloy into bovine serum at 37°C was approximately $0.02 \mu\text{g}/\text{cm}^2$.²¹⁾ The quantity of titanium ions released from the Ti-6Al-4V alloy into 0.17 mol/L NaCl containing 0.0027 mol/L EDTA was approximately $1.0 \mu\text{g}/\text{cm}^2$.²⁰⁾ These results are in close agreement with those obtained in the immersion test. It was suggested that the 1 mass% lactic acid solution was promising as an acceleration solution for immersion testing.

The quantity of titanium ions released from the Ti-15Zr-4Nb-4Ta alloy was much smaller than that released from the Ti-6Al-4V alloy. The quantity of each element released from the three titanium alloys is compared with that of titanium ions released in Figs. 5 to 7. In the 1.2 mass% L-cysteine, 0.05 mass% HCl and 1 mass% lactic acid solutions, vanadium and aluminum ions were released from the Ti-6Al-4V alloy (Fig. 5). In the case of the Ti-6Al-7Nb alloy, the quantity of niobium ions released into the 1.2 mass% L-cysteine or 0.05 mass% HCl solution was smaller than that released into the 1 mass% lactic acid solution (Fig. 6). For the Ti-15Zr-4Nb-4Ta alloy, the quantity of zirconium ions released into

Fig. 5 Quantities of metal ions released from Ti-6Al-4V ELI alloy into 1.2 mass% cysteine, 0.05 mass% HCl and 1 mass% lactic acid solutions at 37°C after one week.

the 1.2 mass% L-cysteine or 0.05 mass% HCl solution was much smaller than that released into the 1 mass% lactic acid solution (Fig. 7). A small amount of niobium ions was released into the 0.05 mass% HCl or 1 mass% lactic acid solution. Moreover, only a small amount of tantalum ions was released into the 1 mass% lactic acid solution.

The ratio of the quantity of titanium ions released from the Ti-15Zr-4Nb-4Ta or Ti-6Al-7Nb alloy to that released from the Ti-6Al-4V alloy (1.0 for control) is shown in Fig. 8. In fetal bovine serum and 1 mass% lactic acid solutions, the quantities of titanium ion released from Ti-6Al-4V and Ti-6Al-7Nb alloys were almost equal. In the 1.2 mass% L-cysteine and 0.05 mass% HCl solutions, the quantity of titanium ions released from the Ti-6Al-7Nb alloy was approximately 75% of that of titanium ions released from the Ti-6Al-4V alloy. The quantities of titanium ions released from the Ti-15Zr-4Nb-4Ta alloy into the fetal bovine serum, 1.2 mass% L-cysteine, 0.05 mass% HCl and 1 mass% lactic acid solutions were considerably smaller, being approximately 30% of that of the titanium ions released from the Ti-6Al-4V alloy.

The ratio of the total quantity of each element other than titanium released from the Ti-15Zr-4Nb-4Ta and Ti-6Al-

Fig. 6 Quantities of metal ions released from Ti-6Al-7Nb alloy into 1.2% mass% cysteine, 0.05% mass% HCl and 1 mass% lactic acid solutions at 37°C after one week.

Fig. 7 Quantities of metal ions released from Ti-15Zr-4Nb-4Ta alloy into 1.2% mass% cysteine, 0.05% mass% HCl and 1 mass% lactic acid solutions at 37°C after one week.

Fig. 8 Comparison of the ratios of quantity for Ti ions released from Ti-6Al-7Nb and Ti-15Zr-4Nb-4Ta alloys to that of Ti ions released from Ti-6Al-4V alloy as control (1.0).

Fig. 9 Comparison of the ratios of total quantity of each element released from Ti-6Al-7Nb and Ti-15Zr-4Nb-4Ta alloys to the total quantity of Al and V ions released from Ti-6Al-4V alloy for control (1.0).

7Nb alloys to that of aluminum and vanadium ions released from the Ti-6Al-4V alloy (1.0 for control) is shown in Fig. 9. In the 1 mass% lactic acid solution, the total quantity of aluminum and niobium ions released from the Ti-6Al-7Nb alloy was larger than that of aluminum and vanadium ions released from the Ti-6Al-4V alloy. It is clear that the total quantities of the elements released from the Ti-15Zr-4Nb-4Ta alloy were much smaller than those of the elements released from the Ti-6Al-4V or Ti-6Al-7Nb alloy.

3.2 Experimental fabrication of implants

Bone plates, artificial hip joints of the cementless type and artificial tooth implants were successfully fabricated with the Ti-15Zr-4Nb-4Ta alloy (Fig. 10). The surface of the bone plate was modified by anodic oxidation. Part of the neck on the stem surface of the artificial hip joint shown in Fig. 10(b) was experimentally fabricated by the same surface treatment used for advanced cementless artificial hip joints made of the Ti-6Al-2Nb-1Ta alloy.^{39,40)}

4. Conclusions

The release of metal ions from the Ti-15Zr-4Nb-4Ta alloy in pseudo body fluids was compared with that from the Ti-6Al-7Nb and Ti-6Al-4V alloys in order to choose an optimum acceleration solution for immersion testing. Bone plates, artificial hip joints of the cementless type and artificial tooth implants were experimentally fabricated using the Ti-15Zr-4Nb-4Ta alloy. The following conclusions were drawn.

The quantities of titanium ions released into the PBS(-), α -medium and fetal bovine serum were much smaller than those released into the 1.2 mass% L-cysteine, 0.05 mass% HCl and 1 mass% lactic acid solutions. It was suggested that 1 mass% lactic acid solution was promising as an acceleration solution for immersion testing. The quantity of the titanium ions released from the Ti-6Al-7Nb alloy was approximately 75% of that of the titanium ions released from the Ti-6Al-4V alloy in 1.2 mass% L-cysteine and 0.05 mass% HCl solutions. Other-

Fig. 10 Bone plate (a), cementless artificial hip joint (b) and artificial tooth implant (c) made of Ti-15Zr-4Nb-4Ta alloy.

wise, the quantities of the titanium ions released from the Ti-15Zr-4Nb-4Ta alloy into the fetal bovine serum, 1.2 mass% L-cysteine, 0.05 mass% HCl and 1 mass% lactic acid solutions were considerably smaller, being approximately 30% of the quantity of the titanium ions released from the Ti-6Al-4V alloy. The quantities of zirconium ions released into the 1.2 mass% L-cysteine and 0.05 mass% HCl solutions were much smaller than that released into the 1 mass% lactic acid solution. The total quantity of zirconium, niobium and tantalum released from the Ti-15Zr-4Nb-4Ta alloy was much smaller than that of the elements released from the Ti-6Al-4V or Ti-6Al-7Nb alloy. Bone plates, artificial hip joints and artificial tooth implants were successfully fabricated with the Ti-15Zr-4Nb-4Ta alloy using conventional manufacturing processes. The new Ti-15Zr-4Nb-4Ta alloy with its excellent corrosion resistance is expected to become the preferential titanium alloy for medical applications in the future.

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