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In vivo metallic biomaterials and surface modification

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Abstract

The chemical properties of metallic biomaterials used for artificial joints, bone plates, and dental implants in vivo are discussed based on empirical data, focusing on the maturation of surface oxide film on titanium and the film's destruction and regeneration in body fluids. It is reviewed the behavior of metallic materials in vivo and how to modify the surface of biomaterials to improve corrosion and wear resistance and bone conductivity. Effect of calcium ion implantation into titanium for improvement of its bone conductivity is given as an example.

Keywords: Metallic biomaterial; Surface oxide layer; Metallic ion release; Titanium; Surface modification

1. Introduction

Materials implanted in vivo initially contact with extracellular body fluids such as blood and interstitial fluid. The chloride ion concentration in plasma is 113 mEq l^{-1} and in interstitial fluid is 117 mEq l^{-1} [1], which may corrode metallic materials. Body fluids contain amino acids and proteins that tend to accelerate corrosion [2,3]. Body fluids also act as a buffer solution and accordingly, their pH changes little. The pH of normal blood and interstitial fluid is 7.35–7.45 [4]. However, the pH decreases to about 5.2 in the hard tissue due to implantation, and recovers to 7.4 within 2 weeks [5]. Thus, corrosion due to an abrupt change in body fluid pH appears negligible. The pH of body fluid near materials may change based on the isoelectric points of biomolecules such as proteins. Whatever the cause, toxicity and allergy occur in vivo if metallic materials are corroded by body fluid, if metallic ions are released into the fluid for a long time, and if ions combine with biomolecules such as proteins and enzymes. Thus, corrosion resistance of metallic biomaterials is important. Currently used biomaterials include stainless steels, cobalt–chromium–molybdenum alloys, commercially pure titanium, and titanium alloys. Alloys recently developed for biomaterials [6,7] also belong to this category.

Reactions on the surface of metals, ceramics, and polymers in vivo differ from each other, although water molecules react with surfaces of all materials. Despite the fact that metallic ion release may be harmful, metals should be used because of their strength, particularly their toughness. Accordingly, their corrosion resistance and hard-tissue compatibility must be improved. This may be realized by a recent progress of ion-beam technology.

We discuss stability and change in surface oxide film on metallic materials inducing the corrosion resistance. Then we consider film destruction and regeneration, metallic ion release and the behavior of metallic ions in body fluids. Finally, we provide improved materials processed by surface modification.

2. Surface oxide film in vivo

Titanium and titanium alloys have good biocompatibility [8] and are currently important biomaterials. Hard-tissue compatibility of titanium depends on its corrosion resistance in vivo, based on passivation [8]. The film consists of amorphous or poorly crystallized and nonstoichiometric TiO_2 [9], and readily regenerates even if destroyed (Fig. 1). Almost no titanium ion release occurs because of high resistance to the destructive action of chloride ions in vivo.

According to passivity theory, the titanium system in aqueous solutions has active and passive surfaces simul-

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taneously in contact with electrolytes [9,10], and undergoes a continuous process of partial dissolution and reprecipitation (Fig. 1), similar to passive film on stainless steel. The passive film composition and properties may thus change with time depending on environments in vivo (Fig. 1). Calcium, phosphorus and sulfur are incorporated in the film on titanium implanted in the jaw bone [11]. Calcium phosphates are precipitated on

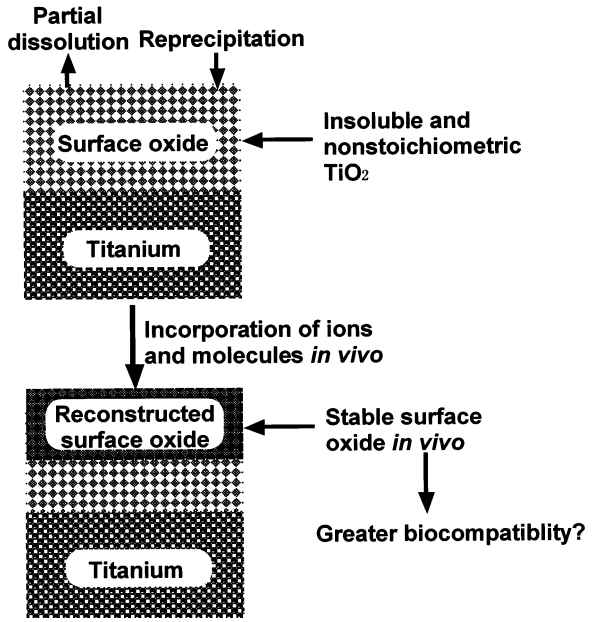

Fig. 1. Schematics of surface oxide film of titanium and film reconstruction in vivo.

Table 1
Precipitates on metals and alloys in Hanks' solution

Metals and alloys (mass %)	Precipitate
Ti Ti–6Al–4V Ti–56Ni	Calcium phosphate
Cr SUS316L Co–30Cr–5Ni Ni–20Cr	Chromium phosphate (later calcium phosphate)
Ti–25Zr	Titanium phosphate Zirconium phosphate (later calcium phosphate)
Ti–50Zr	Titanium phosphate
Ti–75Zr	Zirconium phosphate
Zr	Zirconium phosphate
Au–9Cu–6Ag Ag–20Pd–15Cu–12Au	Chloride
Au	Only hydrated

titanium and its alloys in a simulated body fluid [12–16] (Table 1). The first stage of calcium phosphate formation is the preferential adsorption of phosphate ions [17,18]. Hydrated phosphate ions are adsorbed on a hydrated titanium oxide with the release of protons as follows [13]:

$$Ti(OH)^{3+}_{(ox)} + H_2PO^-_{4\,(aq)} \leftrightarrow Ti^{4+}_{(ox)}HPO^{2-}_{4\,(ads)} + H_2O$$

$$Ti^{4+}_{(ox)}HPO^{2-}_{4\,(ads)} + OH^- \leftrightarrow Ti^{4+}_{(ox)}PO^{3-}_{4\,(ads)} + H_2O$$

or

$$Ti(OH)^{3+}_{(ox)} + HPO^{2-}_{4\,(aq)} \leftrightarrow Ti^{4+}_{(ox)}PO^{3-}_{4\,(ads)} + H_2O$$

where (ads), (ox) and (aq) represent adsorbed ions and ions in oxide and aqueous solution, respectively. Calcium phosphate can be formed by adsorption of calcium ions on the adsorbed phosphates. The Ca/P ratio in calcium phosphates increases and calcium phosphate matures with time.

This phenomenon is specific on titanium and its alloys. On other alloys other phosphate may be precipitated without calcium [12,14] (Table 1). The change in titanium surface in vivo has been observed using high-resolution transmission electron microscopy; proteins are incorporated into the reconstructed surface oxide in addition to calcium, phosphorus and sulfur [19]. The surface oxide film is not always stable and its composition changes through the incorporation of ions and molecules in vivo.

Platinum plating [20] and TiO_2 coating [21] on titanium improve the corrosion resistance but decrease its bone conductivity, i.e. hard-tissue compatibility to titanium depends on both corrosion resistance and surface oxide film reconstruction in vivo.

3. Surface oxide film destruction and regeneration

3.1. Causes of destruction

A surface oxide film on a metal must be destroyed to release metallic ions vigorously. Despite the high corrosion resistance of titanium, titanium is detected in tissue around a titanium implant [22–27], mainly due to repetitive film destruction by wear and fretting. The amount of metallic ions released from a bone plate and screws fixing a fractured bone in a rabbit is much larger than the amount of metallic ions released from those separately implanted in a muscle of the rabbit [28], indicating that wear and fretting between the bone and bone plate and between the bone plate and screws destroy surface oxide film. However, titanium ions are also released from the separately implanted bone plate and screws, due to biochemical factors [25–27], in spite of the absence of wear and fretting.

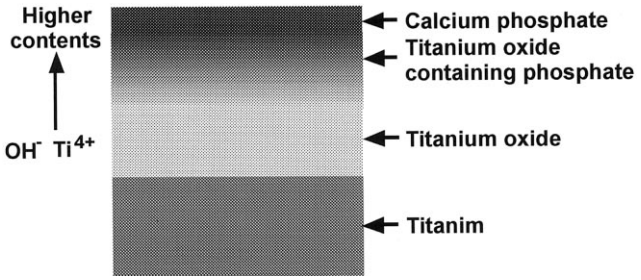

Fig. 2. Schematic cross-sectional view of surface oxide film regenerated in Hanks' solution after mechanical destruction.

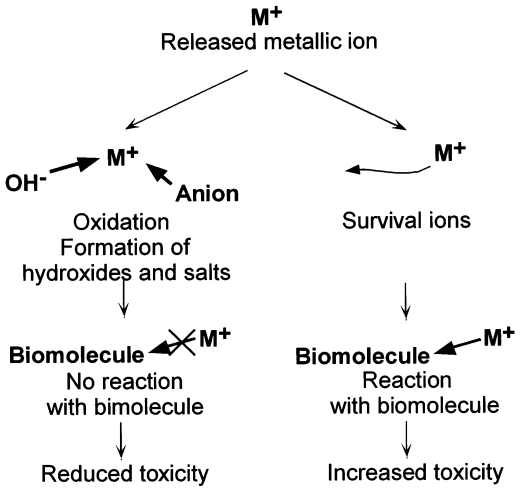

Fig. 3. Behavior of metallic ions released in body fluids.

Amino acids and proteins may be simple biochemical factors in ion release [2,3,29]. Recent research showed that the titanium surface oxide is oxidized by more active oxygen species generated by macrophages adhering to the surface [29]. Macrophages produce O_2^- that readily changes to H_2O_2, which has a much longer lifetime and higher permeability to cell membranes than O_2^- [30–32], i.e. H_2O_2 can reach the surface to which macrophages adhere. The titanium surface is oxidized by H_2O_2 as follows [33]:

$$Ti^{4+} + H_2O_2 \rightarrow Ti^{5+} + OH^- + OH^{\cdot}$$

where $^{\cdot}$ represents a chemical species as a radical. More active oxygen species are generated by macrophages when phagocytosis of wear debris produced from high-density polyethylene used as a socket in artificial hip joints occurs due to macrophages [29]. This mechanism is apparently one of the biochemical factors for the release of titanium ions.

3.2. Surface oxide film regeneration rate

If the surface oxide film is destroyed and remains unrepaired, corrosion proceeds and ion release continues. Metallic ions are released during film regeneration even though film is repaired. Accordingly, the amount of metallic ions released depends on the film regeneration rate, which can be estimated by change in the open circuit potential after mechanical film destruction [34]. Repassivation of titanium in Hanks' solution [34], whose composition and pH are similar to those of extracellular fluid, is slower than that in saline. Thus, the repassivation of titanium in vivo is slower and more titanium ions are released into body fluid. Phosphate ions, existing as $H_2PO_4^-$ and HPO_4^{2-} at the pH we used, are preferentially taken up in the surface film during repassivation. The reaction of phosphate ion incorporation in the surface oxide film is as follows:

$$TiO(OH)_2 + 2H_2PO_4^- \rightarrow TiO(H_2PO_4)_2 + 2OH^-$$

$$TiO(OH)_2 + HPO_4^{2-} \rightarrow TiO(HPO_4) + 2OH^-$$

Therefore, factors delaying film regeneration vary with the material.

3.3. Composition of regenerated oxide film

After mechanical destruction, the surface oxide film regenerated in Hanks' solution contains phosphate ions in the outer layer (Fig. 2). Phosphate ions are preferentially taken up in the surface film during repassivation. Calcium ions are adsorbed on the surface, eventually forming calcium phosphate [34]. The ratio of $[OH^-]/[O^{2-}]$ and the proportion of Ti^{4+} among Ti^{2+}, Ti^{3+}, and Ti^{4+} in the regenerated surface oxide on titanium are larger in the outer surface [34]. Titanium covered by calcium phosphate can be manufactured using the above reaction if the composition of an aqueous lubricant solution for cutting is modified [35]. The composition of the regenerated surface oxide film is similar to that of the precipitate in Hanks' solution.

4. Behavior of released metallic ions

Species bound to titanium ions are highly important from a toxic point of view. Titanium ions react immediately with water molecules and anion species, forming titanium oxide and salts, but hardly with biomolecules (Fig. 3). Comparatively large protein and enzyme molecules hardly react with titanium ions. No biomolecules contain titanium atoms. At the generation of life, titanium atoms should not be incorporated in biomolecules, since titanium could not survive in the primitive ocean as an ion. However, titanium ions easily form complexes with organic ions such as amino acids [36], making titanium ions a possible source of allergy or toxicity. Other ions such as nickel and copper ions survive in body fluids and have a high possibility of combining with biomolecules with a consequent high toxicity. In titanium alloys, component elements such

as nickel survive as ions for a long time, and act as potential allergy or toxicity sources (Fig. 3). The magnitude of toxicity also depends on the type of metallic ion [37].

5. Surface modification

Problems occurring on the surface of metallic biomaterials are best illustrated in the example of an artificial hip joint and bone plate (Fig. 4). Metals are substituted for hard tissue in clinical use. However, metallic ion release and wear debris in artificial joints are serious problems to be solved for safe application. Since metals are essentially nonbiofunctional, their surfaces should be modified to improve corrosion resistance, wear resistance, and bone conductivity [38].

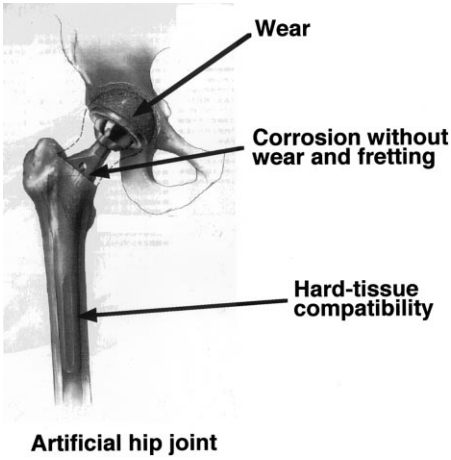

Fig. 4. Possible problems in metallic materials in artificial hip joints.

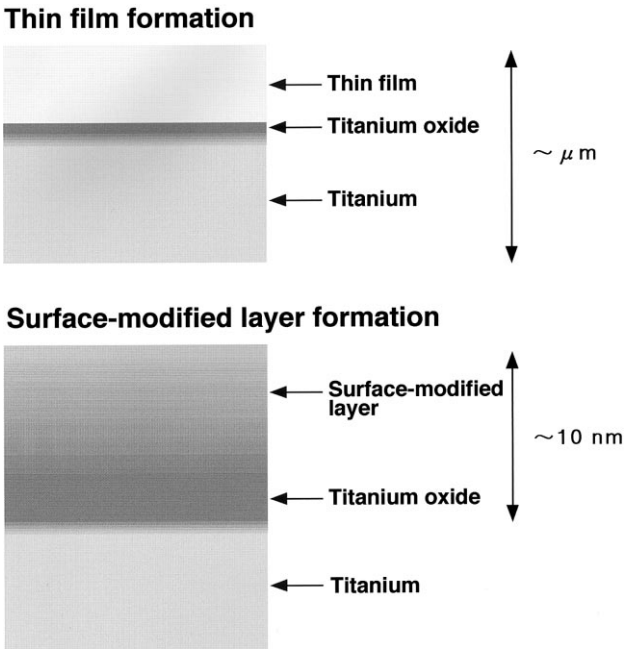

Fig. 5. Cross-sectional illustrations of thin film and surface-modified layer formation for improving bone conductivity of titanium.

Improvement of corrosion resistance is tried by simple high temperature oxidation in air and anodic oxidation in acidic solutions to grow surface oxide. Electrochemical treatments and immersion in alkaline solutions containing calcium and phosphate ions are also performed for the formation of a calcium phosphate layer to increase bone conductivity. Ion beam techniques have recently become a potential method for surface modification.

5.1. Ion-beam surface modification

Ion beam technology has contributed greatly to modifying biomaterial surfaces [39]. The surface modification techniques using ion beam technology are divided into two categories, that is, thin film formation and surface-modified layer formation (Fig. 5).

The thin film formation is used to improve bone conductivity, corrosion resistance, and wear resistance by the formation of apatite film, TiO_2 film, and TiN film, respectively. The film formation technique is easy to control the film composition, but has the disadvantage of a weak adhesion of the thin film to the substrate. Functionally graduated materials are also able to be fabricated by thin film formation technique.

Ion implantation and ion mixing can produce surface-modified layer. Wear resistance and bone conductivity can be improved by nitrogen and calcium ion implantation, respectively. The advantage of these techniques is the formation of virtually graduated composition and an obscured interface between the surface layer and the substrate. This results in the formation of the fracture resistant interface, although the composition control of the surface layer is not easy.

5.2. Surface modification of titanium

The easiest way to increase the corrosion resistance of titanium is anodic oxidation in an acidic solution [40] or high-temperature oxidation in air [41]. Sputter-deposition of thin TiO_2 film [42], is also effective in improving corrosion resistance [43]. By iridium ion implantation into Ti–6Al–4V, electrochemical properties of the alloy approached those of iridium, and corrosion resistance was improved [44,45]. The improvement of corrosion resistance, however, does not always ensure the bone conductivity.

Nitrogen ion is implanted to improve wear resistance and bone conductivity of titanium [46], and to improve corrosion resistance of Ti–6Al–4V [47]. Thin nitride film-formed titanium with high wear resistance [48] is already commercially used in bone plates, dental implants, and artificial hip joints.

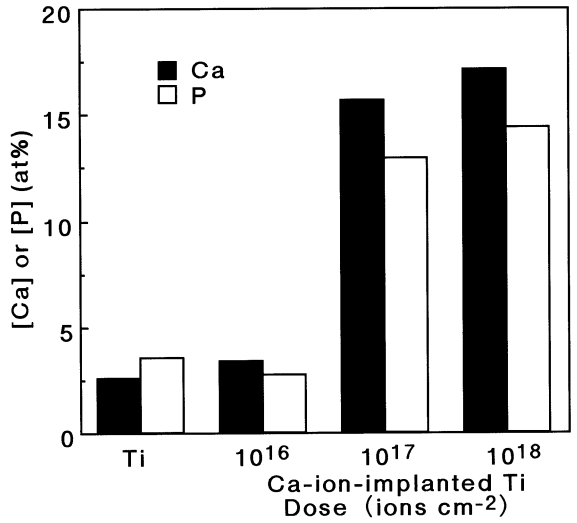

Fig. 6. Concentrations of calcium and phosphorus in calcium phosphates on unimplanted and calcium-ion-implanted titanium specimens immersed in Hanks' solution for 30 d.

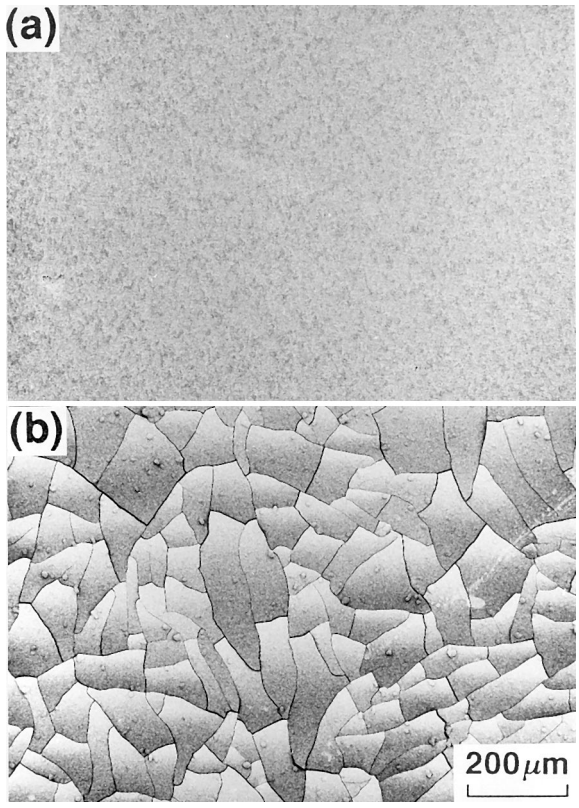

Fig. 7. Scanning electron micrographs of unimplanted titanium (a) and calcium-ion-implanted titanium (b) immersed in Hanks' solution for 30 d.

The most important objective of surface modification of titanium is the improvement of bone conductivity, through formation of a calcium phosphate film. Plasma spraying of apatite on metallic materials is currently widely used to form apatite as nuclei for active bone formation and bone conductivity. For the plasma-sprayed apatite, however, the apatite/titanium interface or apatite itself will be fractured under a relatively low stress because of low joint strength and low toughness of the sprayed layer itself.

Dynamic ion mixing was applied to form apatite with high interface bonding strength [49], where calcium ions are implanted during the mixing process to induce a strong bond between the apatite film and the titanium substrate; implanted calcium ions serve as a binder. Sputter-deposition of apatite has been attempted from the beginning, and RF magnetron sputtering is now used [50]. Immersion [51] and electrochemical treatment [52,53] are also conventionally used to form an apatite film on titanium.

Bone conductivity can be improved by modifying the titanium surface. The formation of titanium oxide gel on titanium by hydrogen peroxide is known to be effective [54]. An titanium oxide gel layer is also formed by immersion in an alkaline solution and heating [55]. Another idea is the formation of oxides containing calcium by immersing titanium in solutions containing calcium ions [56]. Both of these methods also accelerate calcium phosphate precipitation on titanium. Collagen molecules are also coated on titanium to improve the bone conductivity [57].

5.3. Calcium-ion-implanted titanium

Calcium ion implantation into titanium is a promising method for improvement of bone-conductivity of titanium. Fig. 6 shows calcium and phosphorus concentrations in calcium phosphates on unimplanted and calcium-ion-implanted titanium immersed in Hanks' solution for 30 d. Fig. 7 shows scanning electron micrographs of unimplanted titanium (a) and calcium-ion-implanted titanium (b) immersed in Hanks' solution for 30 d. It is clear that calcium-ion implantation accelerates calcium phosphate precipitation on titanium [58]. Osteogenic cells on titanium are activated to form osteoid tissue when calcium ions are implanted [59]. Large amounts of new bones are formed early on calcium-ion-implanted titanium, compared to unimplanted titanium, even two days after implantation into rat tibia [60].

This superiority of calcium-ion-implanted titanium is due to the modified surface by calcium ion implantation. In Fig. 8, the depth-distribution of substances on the calcium-ion-implanted titanium is illustrated schematically. The surface of calcium-ion-implanted titanium consists of calcium titanate when ions are implanted at 10^{16} an9d 10^{17} ions/cm^2, and both calcium oxide and calcium titanate are formed when implanted at 10^{18} ions/cm^2 [61]. The outermost surface in both cases is possibly calcium hydroxide. Calcium ions exist in the surface oxide, which grows with ion implantation. Modified surface layers are very thin; about 6, 8, and 13 nm on specimens implanted at 10^{16}-ions/cm^2,

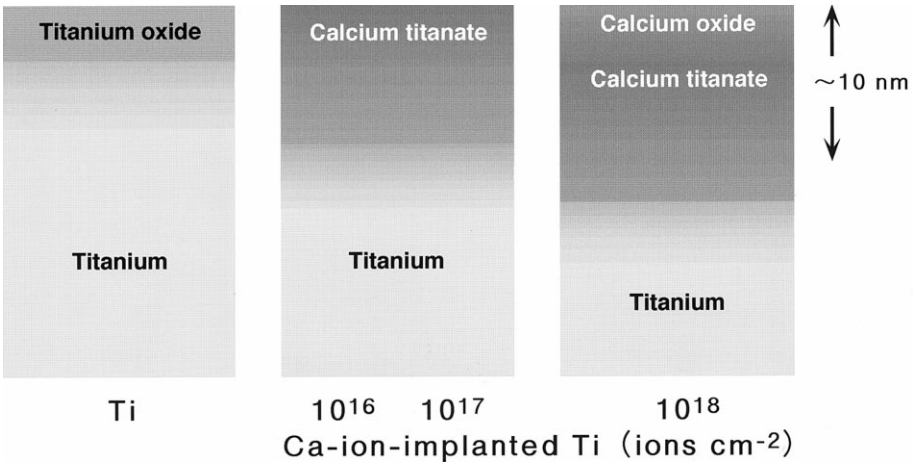

Fig. 8. Schematic illustration of cross-sections of surface-modified layers of titanium specimens with and without calcium-ion-implantation.

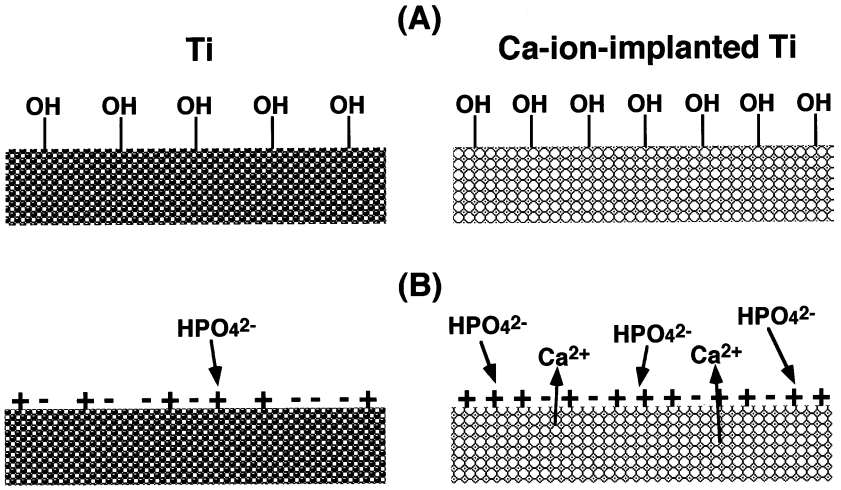

Fig. 9. Hydroxyl radicals (A) in air and (B) electric charges in and body fluid on unimplanted titanium and calcium-ion-implanted titanium.

10^{17}-ions/cm^2, and 10^{18}-ions/cm^2, respectively. This modified layer operates as a substrate with improved hard-tissue compatibility. The calcium-ion-implanted titanium surface is more positively charged by dissociation of hydroxyl radicals than the titanium surface [62] as schematically drawn in Fig. 9, and its number of charging sites is greater. Greater numbers of phosphate ions in body fluid are adsorbed on the calcium-ion-implanted titanium surface because of electric charge attraction, i.e. when the more phosphate ions are adsorbed, the more calcium ions are attracted with the consequent formation of a larger amount of calcium phosphate. Calcium ions are gradually released from the surface of calcium-ion-implanted titanium [63,64] (Fig. 9). This causes supersaturation of calcium ions in the body fluid near the surface, resulting in acceleration of calcium phosphate precipitation.

6. Conclusions

Since metals and alloys have conventionally been considered as structural materials without biofunction, only bioinertia such as corrosion resistance has been required when used in vivo. Even titanium is not always stable in vivo, reacting with ions and molecules and reconstructing the surface oxide film. Understanding of metallic ion toxicity, however, requires knowledge about the amount of ions released, clarification of toxicity itself, and consideration of the probability of combination with biomolecules such as proteins and enzymes. Development of metallic materials having both biofunctions and good mechanical properties will lead to ideal biomaterials. Surface modification such as ion beam technology is thus useful in developing such materials.

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