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Antimicrobial surface modification of titanium substrates by means of plasma immersion ion implantation and deposition of copper

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ABSTRACT

Antimicrobial equipped surfaces of titanium (Ti–6Al–4V) implants are beneficial to prevent implant-associated infections of total joint endoprostheses and osteosyntheses. Copper (Cu) is well suited for this purpose, since it exhibits a well-known antimicrobial activity and can be found as a trace element in the human body, i.e. it is nontoxic in small concentrations. For this approach plasma immersion ion implantation and deposition (PIII&D) of Cu into Ti was evaluated. The amount and also the depth-profile of implanted and deposited Cu in and on the surface were analyzed by X-ray photoelectron spectroscopy (XPS) and ball cratering tests. The layer morphology was studied using scanning electron microscopy (SEM). The surfaces released up to 3.2 mmol/l of Cu within 24 h, measured with atomic absorption spectroscopy (AAS). Such Cu doped and coated Ti implants could be useful for prevention and therapy of implant-associated infections.

1. Introduction

Titanium (Ti) is a material which is well-suited for load-bearing, bone contacting implants. Therefore, it is widely used in orthopedic surgery and dentistry, i.e. for total joint replacements or dental implants. Nevertheless, the osseointegration and the interfacial interaction of the bone with Ti are a topic of interest since many years [1–3]. Because an implant remains a foreign object in the human body its surface has to be biocompatible. It should not provoke adverse reactions, no microorganisms should colonize on it and a fast integration into the functionality of the bone tissue has to be assured.

In particular, the risk prevention of implant-associated infections is a huge challenge in clinical practice. The probability of implant-associated infections e.g. is ca. 2% over the life time of total hip replacements (THR) [4]. At present the total number of THR per year worldwide comes to millions [5,6] and will increase significantly in the next decades due to an aging population and due to advancements in implant and surgery techniques [7]. Hence, the total number of implant-associated infections will clearly increase in the future, regardless of any improved efforts to reduce the incidence [8–10]. This causes high interest in any option to minimize implant associated infections.

Post-operative infections after total joint replacement are either superficial or deep at the periprosthetic bone stock. Superficial infections involve only the wound site and can therefore be treated relatively easy and within the first days after surgery. In contrast to that, deep infections can arise within weeks, months or even after several years after implantation. In the majority of cases the cause is the exogenous transfer of bacteria during surgery [8]. At present, the management of such infections ranges from conservative treatment with antibiotics to complex revision surgery. Typically, substrate interfaces are not easily accessible by antimicrobial substances [11] if bacteria already adhere to the implant surface and form a biofilm [12]. Such biofilms are extremely resistant and activate host defense mechanisms. Therefore the occurrence of biofilms should be prevented by special functionalization of the implant surface.

A number of different strategies have been developed for the modification of implant surfaces to promote the attachment of target tissue cells and to prevent bacterial adhesion and growth simultaneously [13–18]. Inhibition of bacterial colonization can be achieved either by killing the bacteria in the vicinity of the surface or by preventing the bacteria adhesion to the substrate (implant) surface. Hence, the implant surfaces should be modified to possess or release a bactericidal agent. Several approaches were followed in recent years to deal with the Ti implant surfaces. Those can be optimized by coating or doping with metallic ions such as Ag, Cu, and Zn [19–24], by covalent coupling of antibiotics [25–27] or by covalent coupling of antibiotic peptides [28]. By coatings with specific or broad-spectrum antibiotics bacterial colonization can be reduced [29,30], but the implant can display some disadvantages, such as limited adhesion of the agent to the implant surface and the development of bacteria resistances. Therefore, the application of metal-based implant coatings is an interesting alternative approach.

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Positively charged metallic ions are released and subsequently attach to the negatively charged bacterial cell wall; however they can interact with the eukaryote cell wall, the DNA and the proteins present in the cytoplasm and finally cause cell necrosis. Hence, metals and in particular Ag have been found to reveal toxic effects towards human cells as well [31,32]. However, a smaller Ag concentration of 2.05 ± 0.55 wt.% was proven to be both antibacterial and compatible for osteoblasts without cytotoxic effects [31]. Cu is a promising alternative to Ag since it combines good antimicrobial properties with a certain biotolerance regarding to eukaryotic cells [24,33]. In contrast to Ag, Cu is a micronutrient and an essential component of several enzymes and it is not accumulated inside the human body. A relatively high Cu concentration $LD_{50} = 2.3 \times 10^{-1}$ mmol/l is tolerated by eukaryotic MC3T3-E1 mouse fibroblasts (50% toxicity), while the reduction rate of *Staphylococcus epidermidis* growth is 2.5×10^4 [24,34]. However, an increased amount of Cu can also cause cytotoxicity [35–37].

In recent years various methods were investigated for coating, doping or alloying Ti material with antimicrobial effective metals. In particular surface modifications using gas discharge plasmas are a promising approach, since bulk material modification by alloying Ti with Cu fails due to phase segregation in Ti alloys [38]. But, because small amounts of Cu are sufficient for a long-term antimicrobial effect the transfer to the Ti surface can be achieved and controlled by plasma processes more efficiently and homogenously, even for complex shaped substrates. Since a metallic compound is formed, the stability of such an antimicrobial surface is much better than a surface coated by a sol–gel technique [33]. In particular two gas-discharge plasma-based methods, plasma immersion ion implantation (PIII) [39–42] and dual high power impulse magnetron sputtering (dual HiPIMS) [38,43–45], are appropriate to incorporate the necessary amounts of Cu into a Ti surface. The implantation of Cu by PIII is a very interesting approach since it was found to even improve the wear resistance and surface hardness of the Ti substrate while the corrosion resistance was reduced [46].

In this contribution, based on previous studies [37,39,42,47], we present a new approach to generate antimicrobial Ti surfaces generating a short-term burst-release and a long-term release of Cu. Test samples were prepared by means of plasma ion immersion implantation and deposition (PIII&D), a combined method to dope the subsurface and to coat the metallic implant material in one single step.

2. Experimental

2.1. Substrates

The plasma treatments, surface analysis and release measurements were performed with polished Ti alloy disk samples (Ti–6Al–4V, 11 mm diameter, 1 mm thickness, "chemically pure" (cp) quality, roughness of $R_a = 0.019$ μm, provided by DOT GmbH Rostock, Germany).

2.2. Experimental setup

The setup (Fig. 1) is based on an experimental plasma reactor already described in earlier publications [39,42,47]. PIII&D was performed using a radio-frequency (13.56 MHz) excited background plasma which was generated between two coplanar, disk-shaped Cu electrodes of 120 mm diameter and a distance of 160 mm. Both powered electrodes were connected to the radio-frequency (RF) generator (PFG 600 RF, Hüttinger Elektronik, Freiburg, Germany) through a matching network (PFM 1500A, Hüttinger Elektronik, Freiburg, Germany). To achieve homogeneous ion density distribution above the PIII&D electrode, both electrodes were operated with the same voltage without phase shift. The overall consumed power of the background plasma and the power supply was 20 W with a self-bias voltage of about 250 V.

Vaporized water was used as process gas at a pressure of 5×10^{-3} mbar.

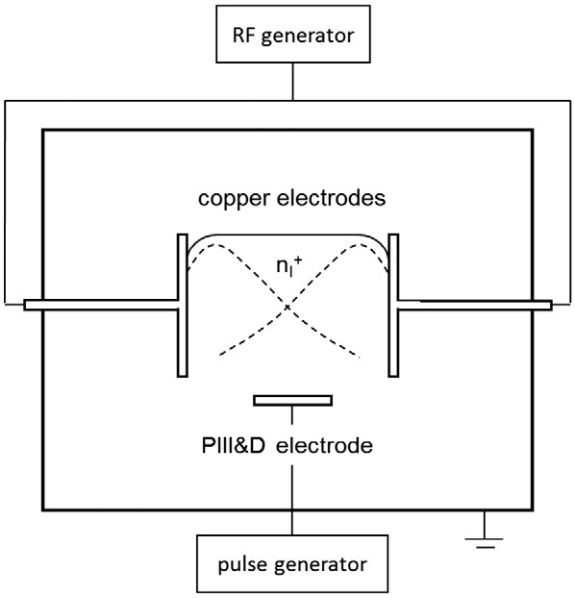

Fig. 1. Experimental setup.

For the present investigations a novel sample carrier made of Cu (60 mm diameter, see Fig. 2) was placed between the two RF electrodes on the PIII&D electrode. It allowed the placement of the Ti samples between tips of Cu cones to create a distance between the Cu sample holder and the Ti disks and potentially implantation and deposition on both sides of the samples.

A pulsed voltage was applied to the sample carrier via a high voltage feed through connected to a pulse amplifier (RUP 3-15A, GBS-Elektronik, Großerkmannsdorf, Germany). The pulse amplifier was operated at 5 kV with up to 48 mA, a repetition rate of 100 Hz and duty cycles from 1% up to 95%. The pulse generation was controlled by a waveform generator (DG535, Stanford Research Systems, Sunnyvale, CA, USA) which delivers square pulses to the pulse amplifier. Ion flux densities to the sample of up to 0.5 mA/cm^2 could be obtained. This led to sample temperatures of up to 600 °C. The treatment time varied between 30 s and 15 min.

2.3. Surface analysis

The elemental chemical composition of the modified surface of the Ti disks was determined by X-ray photoelectron spectroscopy (XPS) (Axis Ultra, Kratos, Manchester, UK) with monochromatic Al K_α

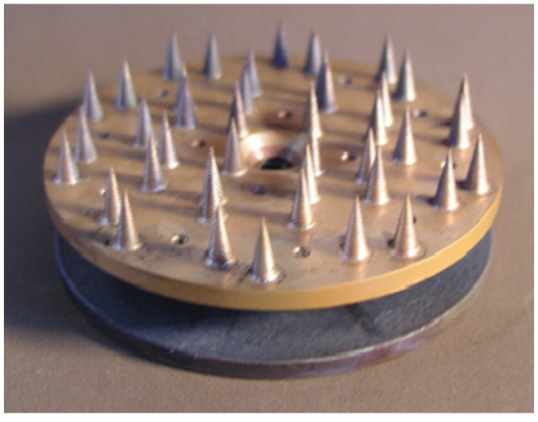

Fig. 2. Illustration of the Cu sample carrier.

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