NiTi coated with oxide and polymer films in the in vivo healing processes

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A B S T R A C T

Plates of NiTi chemically etched, electro-polished, and sol-gel coated with XO2 (X = Ti, Si, Zr), or coated with oxides and dip-coated polymers of Dextro-Levo-lactide-co-glycolide (DL-PLG, 0.4 μm thickness), Dextro-Levo-lactic acid (DL-PLA, 1.3 μm) or poly methyl methacrylate polymer (PMMA, 1.7 μm) were obtained. Smooth and uniform NiTi surfaces without significant pitting, as revealed by AFM, were prepared for chemical etching of 120 s in HF:HNO3:H2O = 1:5:4, followed by electropolishing 120 s in H2SO4:CH3OH:H2O = 1:4:5 electrolyte and using a potential of 9 V. Dip-coated layer of PMMA has shown cracks and large pores and was eliminated from further experiments. Samples of pristine and coated NiTi were in vivo implanted into rabbits and extracted after 10 and 60 days. Clinically, all implants are biocompatible; all rabbits survived and a recovery process was observed for all cases. NiTi covered with SiO2, DL-PLG and SiO2/DL-PLG have shown the best healing evolution. For 10 and 60 days good recovery was found also for NiTi coated with TiO2. Coatings of ZrO2 and ZrO2/DL-PLG have shown the poorest results. The oxide coating and the roughness Rz that contains information on the ‘deep’ large areas in the coatings show the strongest influence on the healing processes. Work indicates the possibility of space- and time- scale controlled variation of the functional properties.

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1. Introduction

1 The quasi-equatomic NiTi alloy [1] has one of the highest shape-recovery-rate among materials exhibiting the shape memory effect. It has also excellent mechanical (supere-

lasticity) and corrosion resistance properties [2]. NiTi was

proved to be a biocompatible material [3]. The shape memory
effect of NiTi alloy promotes designs with changing geomet-
ries depending on temperature, while superelasticity stands
against large displacements. Hence, NiTi alloy is of much inter-
est for fabrication of various medical devices [4]. For example,
the hinge mechanism that it is self-assembled through the
shape memory effect of a constrained or semi-constrained elbow implant simplifies and improves the design and the surgical procedure [5,6]. Other applications are [7,8]: intravascular stents, vena cava filters, orthopaedic compression staples, bone fixation clamps, patellar fixator, shape memory implant used in scoliosis, femoral cup prosthesis, dental arch wire, drug delivery system.

The large amount of Ni content induced a reticence in using the NiTi implants without taking supplementary precautions for avoiding side effects generated by Ni-ion release. Ni induces carcinogenesis [9], and alloys with Ni release of more than 1 μg/cm²/week can give a strong allergy reaction [8]. Though a protective layer of TiO₂ is formed on the surface of NiTi, the Ni surface concentration ranges between 0.4 and 27% [8] and a 10 days in vitro study has shown that there is a Ni release of 5–129 μg/l [8]. To obtain a “zero” side effect of NiTi-implants use, efforts are made to block the Ni/Ti ion leaching by creating a barrier between the implant and the tissue and refs [10–15] show positive results. It is also noteworthy that Liu et al. [10] reported that NiTi coated with a TiO₂ film improves blood compatibility, while Lemaire et al. [13] shows that TiO₂ coating reduces Ni leaching with a factor of 14. SiO₂ and ZrO₂ coatings as effective barriers against Ni leaching were proved by Yang et al. [14], and Sui et al. [15], respectively. A complementary approach is to deposit functional biodegradable films, such as polymers. Biodegradable polymers are themselves of much interest. Studies were made for replacement of permanent metallic stents with fully biodegradable polymeric stents [12,16,17]. Xu et al. studied the biodegradation behaviour of PLGA (poly[lactide-co-glycolide]) stents both in vitro and in vivo for the assessment of the usefulness of biodegradable polymeric stents in human common bile duct repair and reconstruction [18]. On the other hand, Xi et al. [19] investigated the degradation behaviour of a polymeric coating on a cobalt-chromium stent platform. It is also remarkable that biodegradable films can include drugs and during their decomposition they allow their gradual release, significantly improving the recovery processes. Pan et al. [20] used poly[lactide-co-glycolide] (PLGA) as a drug reservoir to develop an emodin-eluting stent by ultrasonic-atomization spraying method. The results were promising, indicating the potential applications of emodin-eluting stents in the treatment of cardiovascular disease. Westedt et al. [11,21] studied the formulation of biodegradable nanoparticles using solvent displacement technique for catheter-based local intraluminal drug delivery. They concluded that PVA-g-PLGA comb polymers are suitable biodegradable polymers for the nan encapsulation of paclitaxel.

Our work proposes a comparative analysis of deposited inorganic, organic and inorganic/organic sandwich-like coatings on a NiTi substrate. Inorganic bio-compatible [14,22,23] coatings consist of an oxide XO₂ (X = Ti, Si, Zr) and organic ones of biodegradable polymers such as poly 2Dextro-Levo-lactide-co-glycolide (DL-PLG), poly 2Dextro-Levo-lactic acid (DL-PLA), and the bio-stable 2poly methyl methacrylate polymer (PMMA). The main role of XO₂ and PMMA coatings is to block the Ni/Ti ion diffusion into tissue and the one of the biodegradable polymeric layer is to carry and deliver the appropriate drugs. As a first step for the assessment of our coatings and to understand the in vivo processes presented in this work, polymers were not loaded with drugs. Nevertheless, our experiments (to be presented elsewhere) indicated that aspirin (acetylsalicylic acid) can be easily incorporated in our polymer coatings as an antplatelet drug. Bare and coated NiTi samples were implanted in rabbits. At the end of the short-term acute (10 days) and long-term chronic (60 days) experiments, samples were extracted and the nearby tissue was investigated. During acute experiments, the temperature of the rabbits was monitored. Coating features vs. their implantation effects are presented and discussed. All rabbits survived the in vivo experiments indicating on the biocompatibility of all materials, but the encountered differences suggest the possibility of space- and time-scale controlled variation of the functional properties.

2. Materials and methods

2.1. NiTi substrate preparation by chemical etching and electropolishing

NiTi shape memory alloy (50.59 at. % Ni) was provided by METAL PRODUCTS Research Institute of Shanghai.

NiTi substrates were smoothened by electrochemical etching, considering that a smooth surface provides an increased corrosion resistance and, hence, the activity of Ni towards interaction with human body can be suppressed. Plates of NiTi with size of approximately 13 mm in length, 4 mm in width and 0.2 mm in thickness were first polished with SiC abrasive paper with an ultrafine grit size of 2000, followed by diamond paste polishing up to the grit size of 8000. After polishing, samples were subject to chemical etching using different ratios of water and acid solutions, and different immersion times. Samples and chemical etching conditions are gathered in the caption of Fig. 1. Surface of the as-prepared NiTi plates was observed by optical microscopy and by tapping-mode atomic force microscopy (AFM, Xetra Prima). Although the Rms (root mean squared roughness), and Rs (roughness based on Japanese Industrial Standard – JIS, taken in 10 points) was not the lowest for sample 4 (immersed in HF-HNO₃:H₂O = 1:5.4 for 120 s, Table 1), this sample was selected for further developments since the surface shows the highest uniformity (visually appreciated over the entire AFM image, Fig. 1(4)) and it has the lowest amount of pits, while their size is reasonably small. Moreover, the peaks in the roughness profile curves (Fig. 1) are rounded, rather than being very sharp as for samples 1 and 2. Sample 3 shows the highest values of Rms and Rs. Rs was calculated by using Eq. (1):

$$R_{\text{RMS}} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} y_i^2}$$

The roughness profile contains ‘n’ ordered, equally spaced points along the trace, and ‘y,’ is the vertical distance from the mean line to the ‘ith’ data point. Height is assumed to be positive in the up direction, away from the bulk material. The average distance typically based on five of the highest peak
and lowest valley over the entire sampling length defines $R_{Z15}$ according to formula:

$$R_{Z15} = \frac{\sum_{i=2}^{s} R_{pi} - R_{vi}}{5}$$

where $R_{pi}$ and $R_{vi}$ are the $i^{th}$ highest peak, and lowest valley, respectively. We observe that $R_{RMS}$ mainly provides information of an average surface roughness (“uniformity”) while $R_{Z15}$ shows the highest variation in the roughness along the measured curve profile and therefore provides information on the ‘deep’ regions from the surface.

The surface finishing of the selected sample 4 was performed by electro-polishing for different conditions of applied voltage and time. Electropolishing conditions applied on etched sample 4 leading to samples denoted 4.1, 4.2, 4.3 and 4.4 are shown in the caption of Fig. 2. The lowest level of pitting corrosion as revealed by optical microscopy (Fig. 2) was encountered for sample 4.4 ($U = 9$ V, 120 s). On the other hand, this sample had the largest $R_{RMS}$ (Fig. 2, Table 2). The value of $R_{Z15}$ was similar to those for samples 4.2 and 4.3 and lower than for sample 4.1. Taking into account the rounded shapes of the peaks in the roughness profile curves expected to promote a better corrosion behaviour, we selected sample 4.4 for subsequent coating steps.

2.2. Sol–gel coatings of $XO_2$ ($X = Ti$, $Si$, $Zr$) on NiTi

Different routes were used for preparation of sol–gels. For $ZrO_2$ we started from aqueous solutions of $ZrOCl_2 + H_2O$. To remove the resulted HCl, amine-formaldehyde resin was added. The water was replaced by distillation with methoxylethan. Finally, a stable ethanolic sol with particles of $ZrO_2$ were obtained. For $SiO_2$ we obtained two solutions by mixing (A) tetraethyl orthosilicate (TEOS), $C_2H_5OH$, and $NH_3-H_2O$, and by mixing (B) TEOS, $C_2H_5OH$, and HCl. The two solutions were mixed ($A + B$), followed by stirring and refluxing. For $TiO_2$ we started from $Ti(OCl_2H_5)$ dissolved in ethyl alcohol, and acetyl acetone was added. A solution of acetic acid, $H_2O$ and ethyl alcohol was added to the previous one. The new solution was stirred, ultrasonicated and kept for 1 week at room temperature, followed by drying at 70°C. More details about concentration of solutions, temperatures, and time are given in [24–26]. The NiTi plates were immersed into the sol–gel solution, extracted with a constant speed of 1 cm/min and
dried at 70°C for 12 h in all three cases. The thickness of the oxide layer was about 90 nm. Both optical and atomic force microscopy indicates that the highest uniformity and the lowest $R_{\text{RMS}}$ and $R_{\text{ZJIS}}$ are obtained for the SiO$_2$ film, followed by TiO$_2$ (Table 3). The poorest surface quality is obtained for ZrO$_2$ (Fig. 3, Table 3).

### Table 2 – Electro-polished samples obtained from the NiTi chemically etched sample 4: roughness measured by AFM. Samples notation is as in Fig. 2.

<table>
<thead>
<tr>
<th>Roughness [nm]</th>
<th>Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{\text{RMS}}$</td>
<td>4.1</td>
</tr>
<tr>
<td>$R_{\text{ZJIS}}$ (10 points)</td>
<td>2.372</td>
</tr>
<tr>
<td>$R_{\text{RMS}}$</td>
<td>16.61</td>
</tr>
</tbody>
</table>

### Table 3 – Sol–gel coated samples: roughness measured by AFM.

<table>
<thead>
<tr>
<th>Roughness [nm]</th>
<th>Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{\text{RMS}}$</td>
<td>TiO$_2$</td>
</tr>
<tr>
<td>$R_{\text{ZJIS}}$ (10 points)</td>
<td>3.103</td>
</tr>
<tr>
<td>$R_{\text{ZJIS}}$ (10 points)</td>
<td>8.484</td>
</tr>
</tbody>
</table>

#### 2.3. Coatings of biodegradable or biostable polymers on Si wafer

A Si wafer (10 mm × 10 mm) for electronics applications was used as a substrate for the experiments of coating with the polymers. This substrate was selected in order to avoid uncertainties regarding the use of a substrate with a different uniformity and roughness (as in the case of oxide coatings)

Fig. 2 – AFM view of the etched NiTi after electro-polishing – surface topography. The electro-polishing parameters are: (4.1) $U = 3$ V for 60 s (Sample 4.1), (4.2) $U = 9$ V for 60 s (Sample 4.2), (4.3) $U = 3$ V for 120 s (Sample 4.3), and (4.4) $U = 9$ V for 120 s (Sample 4.4).

Fig. 3 – AFM images of the sol–gel dip-coated TiO$_2$, SiO$_2$, and ZrO$_2$. 

![AFM images of the sol–gel dip-coated TiO$_2$, SiO$_2$, and ZrO$_2$.](image-url)
obtained in Section 2.2) and of the use of different solvents. The solvents for DL-PLG, DL-PLA and PMMA were ethyl acetate, acetonitrile and dichloromethane [27], respectively. We used DL-PLG biodegradable copolymer ([C₃H₇O₂]₅[C₂H₂O₂]₇) in lactide-glycolide proportion of 85:15, with molecular weight (Mₘ) of 50,000–75,000 g/mol. The rate of hydrolytic degradation of DL-PLG is influenced by copolymer ratio; i.e., 85:15 DL-PLG can be degraded within 5–6 months [28,29]. DL-PLA, with chemical formula (C₃H₆O₂)ₙ, can be degraded within 12–16 months [28,29]. The role of the biostable PMMA coating ([CH₃C(CH₃)(CO₂CH₃)]ₙ, Mₘ = 15,000 g/mol) is of a supplementary organic barrier against Ni dissolution or as a replacement for the oxide coatings [30,31]. The dissolved polymers were ultrasonically stirred (300 W) at room temperature. The samples were immersed in the solutions and dried by evaporating the solvent.

The thickness of DL-PLG, DL-PLA and PMMA polymer coatings on Si was different. Namely, it was about 0.4, 1.3 and 1.7 µm, respectively. Fourier transformed infrared spectroscopy (Jasco FT-IR-6200 Spectrometer coupled with FT-IR Jasco IRT 3000 microscope) measurements (not shown) confirmed formation of the polymer coatings. Surface quality of the polymer coatings was checked by AFM (Fig. 4). PMMA surface has shown cracks and in some regions films were not uniform or continuous. From these reasons PMMA was abandoned and not used in further experiments. By using the same procedure, DL-PLG and DL-PLA polymers were coated on NiTi and NiTi/XO₃ samples.

2.4. In vivo assessments of the implanted samples into rabbits

Healthy 18 rabbits were used for implantation. Their weight was between 1.5 and 1.8 kg. Implants were extracted after 10 and 60 days. Time of the acute and chronic in vivo tests was selected based on the results reported in ref. [3]. Authors of [3] investigated the thickness of the tissue-reaction-capsule surrounding the implant vs. time. They found that thickness of the inflammatory capsule for NiTi implanted in rabbits, decreases reaching saturation for a time longer than approximately 60 days. It was considered that 10 days is appropriate to observe the tissue-implant reaction, while 60 days is the time to reveal the recovery process. All in vivo tests were carried out according with national and European legislation for protection of animals. Surgical preparatory, implantation and explantation steps are presented in Fig. 5a–d, f.

Radiography (Fig. 5e) shows the position of the implants. Before implantation, the implants have been sterilized by

![Fig. 4](image-url) Polymeric dip-coated films of DL-PLG (a), DL-PLA (b), and PMMA (c).

![Fig. 5](image-url) (a) Selection of the incision spots for implantations. (b) Preparation of the surgical area. (c) Insertion of the implants. (d) Suturing. (e) Radiography. (f) Explantation of NiTi implants.
All samples of muscular tissue taken from the adjacent area to the implants were fixed in glutaraldehyde. Optical microscopy images (Fig. 6, Nikon E 600 CCD camera) were taken on the as-prepared samples coloured using the Masson’s trichrome staining protocol. Tissue samples of 60–80 nm thickness were prepared for TEM (transmission electron microscopy) observations using an ultramicrotome and embedding in Epon, according to the standard procedure of Ultrastructural Pathology Laboratory. Contrast enhancement was made with Uranyl Acetate 1% (20 min) and Reynold’s solution (10 min).

3. Results and discussion

All rabbits survived the in vivo tests. We monitored temperature daily, measuring it in the morning and in the evening during the first critical 10 days after implantation. The average temperature and the temperature variation interval for each rabbit are presented in Fig. 7. Temperatures for all rabbits were within the limits for healthy ones [32].

Tissue reaction fibrous capsules (see region B in Fig. 6(h) as an example) can be visualized for all samples in Fig. 6 for a constant magnification. In contact with the living tissue, the biological response is different, depending on the materials type and features at the interface. Three qualitative criteria were considered for tissue evaluation: thickness, smoothness, and the compactness of the contact surface.

The muscular tissue (blue-grey areas in Fig. 6) located in the implant vicinity reacted through a granuloma inflammatory process (red and especially dark red areas in Fig. 6) without a specific association to necrosis. Initial phases of acute/severe inflammation generally developed in the first days after implant insertion. Comparison of the collected implants at 10 and 60 days reveals a chronic inflammation, through the persistence of the inflammatory agent. This is the usual process when stimuli (related to the implanted material which associates with the necrotic tissue occurrence in the surgical
injury) persist or are recurrent. Monocytes-macrophages, lymphocytes and plasma cells were the main cells involved in the inflammation process (Fig. 8). Monocytes that derived from peripheral blood transformed into macrophages. The intensity of cells formation was dependent on the implanted materials and the indicated cells were more often observed in the samples extracted 10 days after surgery. Specific for granuloma tissue is also formation of neo-capillary cells and fibroblast proliferation with collagen depositions. In the samples extracted after 60 days from surgery, granulomatous inflammation elements were found in most cases to contain few macrophage-epithelial cells (isolated or aggregated), lymphocytes, plasma platelets, mastocyte cells, but without multinuclear giant cells. This behaviour is a typical immune response of the host organism. The main resulting cells of the immune response are epitheliotic-type macrophages that may also have a secretory function. The immune response intensity depends on the antigenicity of the introduced materials. Materials in this work are aseptic and neutral so that a necrotic activity was not observed. Worthy to note is also the evolution with the time from surgery of the chronic granuloma elements that is reflected in their fibrous organization with observation of numerous fibroblasts, miobroblasts and with a massive synthesis of collagen and of glucose-aminoglycans as components of the extracellular matrix. The evolution denotes a healing process, but, again, its intensity depends on implanted samples. The differences induced by different samples on contact tissue are addressed in the next paragraphs considering the already mentioned criteria for the reaction fibrous capsules.

For inorganic coatings, the SiO₂ film provides a thin, very smooth, and compact regenerated tissue after 60 days (Fig. 6f, NiTi/SiO₂ 60 days). The thinnest and smoothest contact tissue is observed for the biodegradable DL-PLA layer in the acute experiment (Fig. 6i, NiTi/DL-PLA 10 days). For the chronic experiment the DL-PLG layer (Fig. 6i, NiTi/DL-PLG 60 days) proved to induce a better regeneration than PLGA, where the tissue does not show a good compactness (Fig. 6j, NiTi/DL-PLA 60 days). Finally, the combination SiO₂/DL-PLG shows the best evolution, both for short and long-term experiment (Fig. 6o, p, NiTi/SiO₂/DL-PLG, 10/60 days), hence a good acceptance by the living tissue. A recovery process is detected and, in general, it continues for 60 days (Fig. 6r, NiTi/ZrO₂/DL-PLG 60 days). The encapsulation tissue thickness is stationary (e.g. NiTi, NiTi/DL-PLG, Fig. 6a, b, and k, l) or decreases after 60 days (Fig. 6q, r, NiTi/ZrO₂/DL-PLG). TEM observations (Fig. 8) show that after 60 days, regeneration/healing processes are still visible. Low number of inflammatory cells such as monocytes and macrophages (follow the arrows in Fig. 8) indicate a normal tissue healing activity [33]. At the same time, they show that healing processes are not over after 60 days of implantation.

In summary, there are notable differences among the behaviour of the samples. Considering the thickness/smoothness/compactness qualitative criteria for the inflammatory capsule, our results are gathered in Table 4.

There are situations that are worse at 60 days than at 10 days (Fig. 6, NiTi/ZrO₂/DL-PLG 60 days). Therefore, the implant interface can either accelerate the healing response, or delay it. This observation shows that certain films on the implant can play an important role in tissue regeneration. The factors

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**Fig. 7 – Monitored rabbits’ body temperatures during the acute experiment.**

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**Fig. 8 – Selected TEM images showing healing traces. (a) Bare NiTi sample. (b, c) NiTi/TiO₂ sample, (d-f) NiTi/SiO₂ sample, (g) NiTi/PLA sample (PG – proteoglycans, # – collagen, FB – fibroblasts, * – degranulation, PC – plasmocytes, LS – lysosomes, MP – macrophages, PMN – polymorphonuclear, GC – granulocyte, AEM – amorphous extracellular matrix, MC – monocytes, 9100 x).**
influencing regeneration processes are known to be multiple. Due to complexity it is not possible to establish confidently the key factors and observed correlations can be local fitting only a certain case. Bearing in mind this important observation, we shall remind that Figs. 3, 4 and Table 3 revealed different patterns and qualities of coated films. Results suggest that materials and surface details play an important role in the implant-tissue interaction. The effects of the material type and of the surface patterns cannot be separated. Nevertheless, our data may give some hints concerning the major influence for our specific samples. In our assessment analysis we started from the assumption that corrosion processes can be suppressed for a lower roughness of the surface. The possibility of a controlled corrosion on a space and time scale is expected to provide the background for a better healing process (e.g. faster, easier and more predictable without complications). In Sections 2.2 and 2.3 we have noted that one has to discuss the surface patterns of our films from the viewpoint of a macro and micro roughness somehow revealed by $R_{ZIS}$ and $R_{RMS}$. Moreover, we also pointed out that in the roughness profile curves may show sharp or rounded shapes. All these details may contribute to corrosion and bio processes at interface. For the oxide coatings and to a less extent for the oxide/polymer coatings the influence of the oxide coating seems to be essential (Table 4). A strong influence is given by the oxide coating surface quality: the lowest $R_{ZIS}$ and $R_{RMS}$ values for SiO$_2$ and the highest for ZrO$_2$ are in agreement with the best healing results for the first oxide and with the poorest one for the second oxide, respectively. We have seen that a coated film is composed of smooth areas mainly described by $R_{RMS}$ and large ‘deep’ circular areas stronger involved in estimation of $R_{ZIS}$. One observes from Table 4 that, while the variation of $R_{RMS}$ for TiO$_2$ and ZrO$_2$ (Table 3) is small (3.103 and 3.393 nm), a better healing process is for sample TiO$_2$ with a lower $R_{ZIS}$ (4.108 nm for TiO$_2$ and 16.21 nm for ZrO$_2$) and less ‘deep’ type areas. The result evidences the strong influence of the ‘deep’ areas on recovery processes and further research is necessary. As regarding the polymer layer, it also shows a morphology (Fig. 4) resembling the one for the oxide coatings. The ‘deep’ areas in the polymer case are often pores. While they can also influence the healing processes at interface on space and time scale depending on their distribution and size, they can be useful for designing of the drug-eluting films.

<table>
<thead>
<tr>
<th>No.</th>
<th>Implant</th>
<th>Acute (10 days)</th>
<th>Evolution</th>
<th>Chronic (60 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiTi</td>
<td>*</td>
<td>→</td>
<td>**</td>
</tr>
<tr>
<td>2</td>
<td>NiTi/TiO$_2$</td>
<td>***</td>
<td>→</td>
<td>***</td>
</tr>
<tr>
<td>3</td>
<td>NiTi/SiO$_2$</td>
<td>*</td>
<td>→</td>
<td>**</td>
</tr>
<tr>
<td>4</td>
<td>NiTi/ZrO$_2$</td>
<td>**</td>
<td>→</td>
<td>*</td>
</tr>
<tr>
<td>5</td>
<td>NiTi/DL-PLG</td>
<td>*</td>
<td>→</td>
<td>***</td>
</tr>
<tr>
<td>6</td>
<td>NiTi/DL-PLA</td>
<td>***</td>
<td>→</td>
<td>*</td>
</tr>
<tr>
<td>7</td>
<td>NiTi/TiO$_2$/DL-PLG</td>
<td>***</td>
<td>→</td>
<td>**</td>
</tr>
<tr>
<td>8</td>
<td>NiTi/SiO$_2$/DL-PLG</td>
<td>*</td>
<td>→</td>
<td>*</td>
</tr>
<tr>
<td>9</td>
<td>NiTi/ZrO$_2$/DL-PLG</td>
<td>**</td>
<td>→</td>
<td>*</td>
</tr>
</tbody>
</table>

**Table 4 – Implant-tissue qualitative evaluation after acute and chronic experiments (conventional notation: * = poor, ** = average, *** = best).**

4. Conclusion

From a clinical viewpoint, all implants show good in vivo biocompatibility. All rabbits survived to the experiments and a good recovery process was observed for all cases. NiTi samples coated with SiO$_2$, DL-PLC, SiO$_2$/DL-PLG have shown the best results for the recovery progress. Good results for the short and long experiments were also observed for NiTi/TiO$_2$. Coatings of ZrO$_2$, DL-PLA and ZrO$_2$/DL-PLG have shown the poorest results in the long-term experiment. The possibility of space and time scale controlled healing processes by using suitable coatings is envisioned. Materials and surface patterns of the samples at interface show a strong influence on the recovery processes. Oxides and especially ‘deep’ areas reflected by roughness $R_{ZIS}$ are the strongest factors influencing healing processes.

**Conflicts of interest**

The authors declare no conflicts of interest.

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