**Nanohydroxyapatite in a PDLLA surface coating conducts bone formation on porous coated titanium implants.**

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**Introduction**

Development in the area of biocompatible materials is constantly pushed forward in performance and complexity by research inspired by structure and function of living tissue. Not only is the research aimed at avoiding counteractive tissue reactions to the material, but also at conducting a specific tissue response, e.g. formation of bone tissue – a property referred to as osteoconduction.

The use of hydroxyapatite (HA) in orthopedic devices such as joint prostheses, bone grafts and scaffolds is a well established approach for providing osteoconductive properties. Joint prostheses coated with HA benefit from these properties by increased integration within the bone bed. Recent studies in development of a drug releasing biodegradable polymer coating have introduced a new approach for providing osteoconduction to implant surfaces. Different compounds (growth factors, antibiotics & bisphosphonates) have a reported impact on the periimplant environment when released from the coating.

Although promising as local drug delivery system, little attention has focused on the osteoconductivity of the polymer coating itself. In this study particulate HA is added to the polymer to introduce osteoconductivity to the otherwise inactive coating.

**Methods**

A composite coating of poly-D,L-lactic acid (PDLLA) and particulate HA sized 20 – 70 nm in a 50/50 vol% was developed, characterized and compared to a pure PDLLA coating. A dip-coating technique applicable for any surface was used. The particles were characterized with transmission electron microscopy (TEM) and the coatings with atomic force microscopy (AFM) and scanning electron microscopy (SEM).

Approval was obtained from the local Animal Care and Use committee to commence an in vivo sheep study. The coatings were applied to small cylindrical titanium implants and tested in a non-weight bearing 2 mm gap implant model (Fig. 1). The animal study design was paired. Ten domestic sheep had implants inserted bilaterally in the proximal humerus (Fig. 1) to make each animal its own control. The observation time was 12 weeks. To evaluate coating osteoconductivity the implants were exerted to push-out tests and the periimplant tissue to histomorphometric analysis. The push-out test directly measures fixation stiffness, maximum shear strength and total energy needed to displace the implant from periimplant tissue. The histomorphometry distinguishes and quantifies mineralized bone, fibrous tissue and marrow tissue on the implant surface and in the gap.

The data could not be assumed normally distributed and non-parametric statistics were used for hypothesis testing. A p-value less than 0.05 was considered significant.

**Results**

Size and crystal lattice of HA particles was confirmed with TEM. The PDLLA/HA coating was characterized with AFM as a homogeneous dispersion with HA-particles presented on the polymer surface (Fig. 2). SEM pictures confirmed similar coating thicknesses. The coatings were partly resorbed during the observation time. Remains of both coatings were present on 20% of the implant surfaces. Implants coated with the composite were partially covered with a layer of newly formed bone (39.3%) and primarily fibrous tissue for the remainder (Tbl. 1). The pure PDLLA coating, however, was covered almost completely with fibrous tissue (Tbl. 1). Consequently the composite coating resulted in a significantly better mechanical stiffness, energy (Tbl. 1) and strength of fixation. The coatings had no apparent impact on tissue formed in the 2 mm gaps. Both around composite and pure polymer coatings the gaps were filled primarily with marrow tissue and smaller amounts of fibrous tissue. No bony ingrowth into the gap from surrounding bone was observed, and accordingly no bony bridging to the implant was present. The most important results of the push-out tests and histomorphometry are listed in table 1.

**Discussion**

Adding HA particles to PDLLA increased osteoconductivity compared to pure PDLLA. The result is in agreement with previous studies of composites intended for tissue engineering. A PDLLA/HA composite scaffold was recently reported osteoinductive – i.e. capable of nucleating bone formation in an extraosseous implant site. Although not osteoinductive by definition the composite coating tested in this study did induce nucleation of new bone independently of existing bone. A notable amount of fibrous tissue (Tbl. 1) was also present on the implants indicating adverse tissue reaction besides the osteoconduction. The lagging ingrowth from surrounding bone bed is, as opposed to distant effects of the coatings, more likely a result of choosing the gap to large for a test animal with low bone regeneration.

PDLLA/HA composite coatings need further investigation to elaborate potential clinical application. In contrast to clinically available HA coatings the composite could be extended with addition of bone active compounds and furthermore degrade faster to allow earlier ingrowth to the implant surface.

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**Figure 1.** Experimental gap implant in the proximal humerus in an oversized drill hole.

**Figure 2.** AFM scans of pure PDLLA (left) and PDLLA/HA composite (right). The HA particles are dispersed in the composite matrix, whereas no features are seen on the pure PDLLA. Scale: 2*2 µm.

**Table 1.** Push-out test (1st & 2nd column) and histomorphometric (3rd & 4th column) results. NB – new mineralized bone, FT – fibrous tissue. Median (interquartile range). P-value < 0.05 is denoted (*)

<table>
<thead>
<tr>
<th></th>
<th>Energy (J/m²)</th>
<th>Stiffness (MPa/mm)</th>
<th>NB on surface(%)</th>
<th>FT on surface(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>110* (23-369)</td>
<td>7.2* (0.4-16.2)</td>
<td>39.5* (37-42.8)</td>
<td>58.3* (56.2-61.8)</td>
</tr>
<tr>
<td>Polymeric</td>
<td>11 (0-20)</td>
<td>0.07 (0-0.2)</td>
<td>0.2 (0.16-0.42)</td>
<td>96.2 (91.4-97.9)</td>
</tr>
</tbody>
</table>

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