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Histological and biomechanical evaluation of phosphorylcholine-coated titanium implants

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Abstract

Objective: Compounds considered for drug delivery from oral implant surfaces in support of local bone formation might themselves influence osseointegration. Phosphorylcholine (PC) polymers have been shown to enhance the biocompatibility of medical devices and to serve as drug delivery systems. The objective of this study was to evaluate local bone formation and osseointegration at PC and positively charged PC (PC+)-coated endosseous implants in an established rabbit model.

Material and Methods: Sixteen adult female New Zealand White rabbits were used. Eight animals received PC-coated and control titanium porous oxide surface implants placed in the left and right distal femural condyle (trabecular bone) and proximal tibial metaphysis (cortical bone) using aseptic routines. The remaining eight animals similarly received PC+ and control implants. One implant was placed in each femural condyle and two implants in each tibial metaphysis. Experimental and control implants were alternated between the left and right hind legs. Fascia and skin were closed in layers. The animals were euthanized following a 6-week healing interval for biomechanical (removal torque) and histometric analyses.

Results: Peri-implant bone density was considerably greater at tibial compared with femoral sites within as well as immediately outside the implant threads. However, there were no significant differences in bone density among PC, PC+, and control implants. Nevertheless, bone–implant contact was significantly lower at PC compared with PC+ and control implants in cortical bone ($p < 0.05$). Numerical differences in trabecular bone did not reach statistical significance. The removal torque evaluation revealed significantly lower values for PC compared with PC+ and control sites ($p < 0.05$).

Conclusion: The histometric and biomechanical analyses suggest that PC coating may influence biological processes and ultimately osseointegration of endosseous implants. Apparently, incorporation of cationic charges may reverse or compensate for this scenario. Nevertheless, both PC coatings exhibited clinically acceptable osseointegration. In perspective, PC technology appears to be a viable candidate delivery system for agents in support of local bone formation at endosseous implant surfaces.

Key words: osseointegration; phosphorylcholine; rabbit model; tissue engineering; titanium

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Conflict of interest and source of funding statement

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Phosphorylcholine (PC) is the chemical head group found in the inner and outer layers of lipids forming cell membranes (Lewis 2000, 2006, Iwasaki & Ishihara, 2005). PC contains positive and negative charges and is electrically neutral (zwitterionic) over a wide pH range. As the predominant head group present in the lipids of the outer cell membrane layer, PC plays a key role in determining how cells interact. The zwitterionic nature of PC, combined with its ability to bind water tightly, provides PCs with a significant resistance to non-specific and irreversible adhesion of proteins (Ishihara et al. 1998, Lewis 2000).

Because protein adhesion represents the initial biological process that may jeopardize the biocompatibility of implantable medical devices, PC has the potential to decrease this adverse biological response to a series of materials (Lewis 2006). PC polymers have been shown to enhance the performance of medical devices, reducing thrombogenicity (Lowe et al. 2005), inflammatory response (Goreish et al. 2004), and bacterial adhesion (Russell 2000). Synthetic PC polymers are being evaluated or used within a number of biomedical technologies including contact lenses, coronary and ureteric stents, nephrostomy tubes, and cardiopulmonary bypass and catheter systems (Lewis 2006). PC polymers have also been used for local drug delivery of oestrogen (New et al. 2002), dexamethasone (Patti et al. 2005), and antiproliferative agents (Buellesfeld & Grube 2004). Specific chemical properties and molecular architectures can be achieved using different polymerization techniques to synthesize PC polymers (Lewis 2006). In this regard, the interstitial space can be controlled, affecting drug diffusion; hydrophobic domains and cationic charges can be incorporated to modulate the release of drugs with different properties.

PC polymers have the ability to reduce protein adsorption-limiting biological responses to the materials (Ishihara et al. 1998). However, for some medical devices cell adhesion and host–device interaction are beneficial biological events. Endosseous oral implants need close contact with surrounding cells and tissues to achieve osseointegration. An alternative to accelerate protein adsorption, cell adhesion and growth to PC polymers is the incorporation of a cationic charge into the material surface (Lewis et al. 2004, Rose et al. 2004). This could enable the use of these polymer coatings with endosseous oral implants, in particular, for the delivery of polypeptide growth and differentiation factors in support of local bone formation. The objective of this study was to evaluate local bone formation and osseointegration at PC and positively charged PC (PC+)-coated endosseous implants in an established rabbit model.

Material and Methods

Sixteen adult, female New Zealand White rabbits, approximate weight 3.5 kg, were used following a protocol approved by the local animal ethics committee. The left and right distal femoral condyle and proximal tibial metaphysis served as experimental sites. The femoral condyle represents a bone morphology similar to that of the human posterior maxilla, i.e. sparsely trabecular bone. The tibial metaphysis lacks trabecular bone consisting mainly of cortical bone and marrow.

Two experimental implant surfaces, PC and positively charged PC (PC+) (PC Technology™, Biocompatibles International, Farnham, UK), were evaluated and compared with a commercially available control surface. Experimental implants ($\varnothing 3.75 \times 7$ mm; TiUnite™, Nobel Biocare, Göteborg, Sweden) were coated with PC (PC1036) and PC+ (PC2028) using proprietary technology and were delivered sterile to the surgical laboratory. Control implants featured the same characteristics as the experimental implants without PC/PC+ coating.

Surgeries were performed using aseptic routines. General anaesthesia was induced using a fluanison-fentanyl blend (Hypnorm™, Leo, Helsingborg, Sweden; 0.5 ml/kg i.m.) and diazepam (Apozepam™, Alpharma, Stockholm, Sweden; 0.25 mg/animal i.p.). Lidocaine infiltration anaesthesia was used at the surgical sites (Xylocaine®, AstraZeneca, Södertälje, Sweden; 2 ml). The sites were shaved, disinfected, and accessed using incisions through the skin and fascia. The bone surfaces were exposed using an elevator. Implants were placed following site preparation using saline-cooled 2- and 3-mm twist drills, followed by screw tapping. Three experimental and three control implants were placed in each animal. One implant was placed in each femoral condyle and two implants in each tibial metaphysis. Thus, each animal received six implants: two in femoral and four in tibial sites. Experimental and control implants were alternated between the left and right hind legs. Fascia and skin were closed in layers. The animals were euthanized following a 6-week healing interval using an overdose of anaesthesia.

Based on extensive experience with this animal model, eight duplications of each experimental/control condition and evaluation technique have been shown to be necessary for the statistical analysis. Thus, eight animals received PC/control implants and eight animals received PC+/control implants in contralateral sites. Implants placed in tibial sites were analysed using removal torque (eight PC/control, eight PC+/control) and histology (eight PC/control, eight PC+/control), and implants placed in femoral sites (eight PC/control, eight PC+/control) were analysed using histology.

Removal torque analysis was performed as described previously (Sennerby et al. 2005). Briefly, a specially designed rig with a motor-driven device was used to produce a linear increasing torque applied until integration failure. The peak value was recorded in Ncm.

The second experimental and control tibial implant and the femoral implants for each animal were processed for histologic evaluation. The fixated specimens (10% buffered formalin) were dehydrated in a graded ethanol series and embedded in light-curing methacrylate (Technovit 7200 VCL, Kulzer, Wehrheim, Germany). The implants were cut in a mid-axial coronal–apical plane using the ''sawing & grinding technique'' (EXAKT Apparatebau, Norderstedt, Germany) and were subsequently ground and polished to a final thickness of approximately 10 μm (Donath & Breuner 1982, Rohrer & Schubert 1992). The sections were stained with toluidine blue.

One masked, calibrated examiner performed the histometric analysis using incandescent and polarized light microscopy (BX 60, Olympus America Inc., Melville, NY, USA), a microscope digital camera system (DP10, Olympus America Inc.), and a PC-based image analysis system (Image-Pro Plus™, Media Cybernetic, Silver Springs, MD, USA). The most central section for each implant was used for the histometric analysis. The following measurements were recorded:

- *Bone density outside the threads* (BD_{OT}): ratio bone/marrow spaces immediately outside the implant threads in the adjoining the resident bone (Fig. 1).
- *Bone density within the threads* (BD_{WT}): ratio bone/marrow spaces inside the implant threads in the adjoining the resident bone (Fig. 1).
- *Osseointegration*: percentage of bone–implant contact measured within the area of cortical (tibia) and trabecular (femur) resident bone.

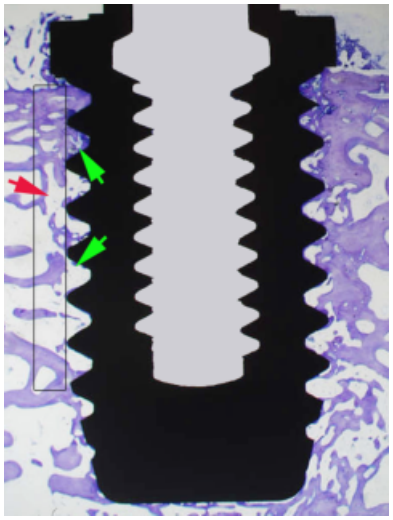

Fig. 1. Representative photomicrograph illustrating bone density assessment within and outside the threads. Assessment of bone density within the threads (BD_{WT}; green arrows) entailed bone density within the resident bone along the entire threaded area of both sides of the implant. Bone density outside the threads (BD_{OT}; red arrow) entailed bone density within the resident bone in a field immediately outside the threaded area corresponding in length and depth to the threaded area (outlined).

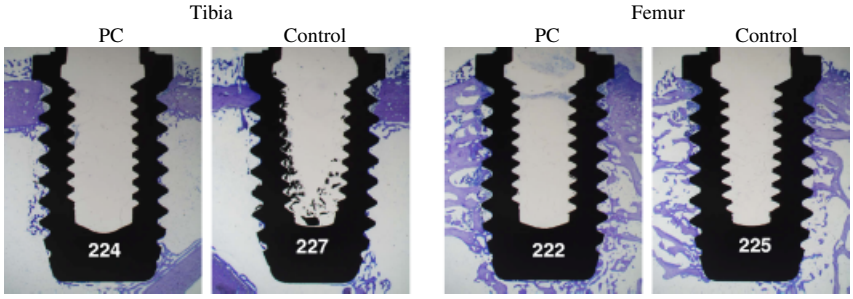

Fig. 2. Representative photomicrographs of implants coated with phosphorylcholine (PC) and control.

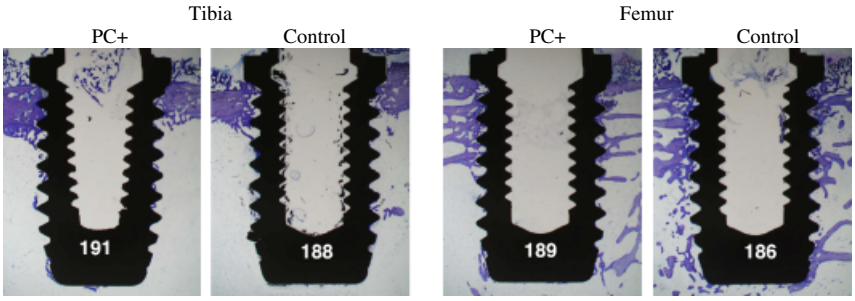

Fig. 3. Representative photomicrographs of implants coated with positively charged phosphorylcholine (PC+) and control.

The statistical analysis was performed using Stata 9.2 for Windows (Stata Corporation, College Station, TX, USA). Linear models were used to compare the experimental and control groups. Clustering of observations within animals was accounted for using appropriated variance estimators. Significance was set at 5% and *p*-values were adjusted for multiple comparisons. Control groups were compared and because no differences were observed they were pooled for analysis purposes. Means (± SE) are presented.

Results

Representative central sections subject to the histologic evaluation are shown in Figs 1–3. The descriptive histologic analysis showed that tibial sites exhibited cortical bone with some new bone formation associated with the implants. There were no apparent differences between sites receiving PC, PC+, or control implants. Similarly, there were no remarkable differences among PC, PC+, and control implants placed in femoral trabecular bone.

The results of the quantitative histologic analysis are shown in Tables 1 and 2. Peri-implant bone density was considerably greater at tibial than at femoral sites within as well as immediately outside the implant threads. There were no significant differences in bone density among the groups; PC, PC+, and control implant specimens all exhibited similar bone density relative to location, i.e. tibial or femoral sites. However, bone–implant contact was significantly lower at PC compared with PC+ and control sites in cortical bone ($p < 0.05$), whereas numerical differences between PC and PC+ and control implants did not reach statistical significance in trabecular bone ($p > 0.05$). The results from the removal torque evaluation are shown in Table 3. Removal torque values for PC sites were significantly lower than that observed for control and PC+ sites ($p < 0.05$).

Table 1. Bone density outside (BD_{OT}) and within (BD_{WT}) the threads, and bone–implant contact (BIC) for implants placed in cortical bone (tibia)

	BD_{OT} (%)		BD_{WT} (%)		BIC (%)	
	mean	SE	mean	SE	mean	SE
PC	89.8 a	1.0	62.0 a	2.6	46.0 a	5.5
PC+	87.8 a	2.2	71.3 a	4.9	61.4 b	5.7
Control	86.8 a	1.5	63.5 a	2.7	59.8 b	3.6

Means followed by the same letter do not differ significantly ($p > 0.05$).
PC, phosphorylcholine.
PC+, positively charged phosphorylcholine.

Discussion

The present study was conducted to evaluate the influence of PC technology on implant fixation using a rabbit model. Compared with control and PC+-coated implants, bone–implant contact was significantly smaller at PC-coated implants placed in tibial sites, as was the removal torque force. Differences between implant surfaces did not reach statistical significance at femoral sites. The histometric and removal torque analysis may suggest that the PC coating deferred biological processes including fibrin clot adsorption/adhesion/maturation and cell adhesion/attachment, ultimately influencing osseointegration of the implants. The PC+ coating apparently reversed this scenario; the incorporation of cationic charges may have increased

Table 2. Bone density outside (BD_{OT}) and within (BD_{WT}) the threads, and bone–implant contact (BIC) for implants placed in trabecular bone (femur)

	BD_{OT} (%)		BD_{WT} (%)		BIC (%)	
	mean	SE	mean	SE	mean	SE
PC	66.3 a	2.2	49.4 a	4.9	48.2 a	4.5
PC+	63.7 a	3.2	50.8 a	3.5	57.2 a	4.7
Control	65.2 a	2.1	53.1 a	3.3	57.4 a	3.2

Means followed by the same letter do not differ significantly ($p > 0.05$).
PC, phosphorylcholine.
PC+, positively charged phosphorylcholine.

Table 3. Removal torque for implants placed in cortical bone (tibia)

	Removal torque (Ncm)	
	mean	SE
PC	24.9 a	2.0
PC+	26.8 b	3.4
Control	33.1 b	1.7

Means followed by the same letter do not differ significantly ($p > 0.05$).
PC, phosphorylcholine.
PC+, positively charged phosphorylcholine.

protein adsorption/adhesion and subsequent cell adhesion to the PC surface (Rose et al. 2004).

Implant stability represents one prerequisite for successful oral implant-based prosthetic reconstruction. Implant stability can be separated into primary and secondary stability. Bone density, surgical preparation, and implant design govern primary implant stability. Secondary stability is pending the biologic response to the implant during osseointegration and functional loading (Jovanovic et al. 2003). In addition to functional loading, secondary stability may be influenced by surface modifications intended to support local bone formation and osseointegration (Huang et al. 2005, Xiropaidis et al. 2005, Becker et al. 2006, Qahash et al. 2007). Thus, several techniques and materials intended to modify the implant surface have been proposed and evaluated. Surface modification can be achieved by physically changing the titanium outer layer or by adding or removing material and biomolecules to the implant surface. To the best of our knowledge, this is the first study to evaluate the PC technology applied to endosseous titanium oral implants. PC technology could be used as a stand-alone technology or as a carrier technology combined with various agents including growth and differentiation factors, and may thus have the potential to enhance clinical outcomes.

As a stand-alone technology, PC use would be based on the high biocompatibility that it can confer to coated materials. Implant biocompatibility is a key characteristic to achieve osseointegration, and surface modification with PC could facilitate and/or improve osseointegration. In this study, however, reduced bone–implant contact and removal torque forces were observed for the PC-coated implants compared with control. A possible explanation for this finding may relate to a reduced adsorption/adhesion of blood clot elements to PC-coated surfaces due to PC's high affinity to water and low affinity for proteins and glycoproteins (Iwasaki & Ishihara 2005). However, it is unlikely that the relatively small decrease observed in bone–implant contact and removal torque resistance is of clinical significance. The observation that PC+ coatings exhibited increased osseointegration provides assurance that the PC coating per se can be manipulated to optimize osseointegration.

PC technology could also be used as part of drug delivery systems also including growth or differentiation factors for enhanced local bone formation (Hall et al. 2007). Studies have shown that PC can be used for controlled release of dexamethasone and oestrogen in coronary stents, while retaining its integrity as a coating material (New et al. 2002). This technology could potentially be used for delivery of bone morphogenetic proteins or other bone growth factors. Besides inducing bone formation, this technology could also be used to deliver bone metabolic agents including bisphosphonates to prevent or retard bone resorption following implant placement (Wermelin et al. 2007). If growth or differentiation factors or other metabolic agents may successfully be released from a drug delivery system that uses PC technology, this might overcome any initial decrease in implant stability experienced in controlled clinical settings (Glauser et al. 2004).

It must be realized that the control, the oxidized titanium implant surface used in the present study, exhibits an unusually high order of osseointegration approximating 70% as estimated both in Type II and IV bone using discriminating large animal models (Huang et al. 2005, Xiropaidis et al. 2005); thus, the somewhat lower osseointegration estimates for the PC coating in this rabbit screening model may still be well within the scope of clinical relevance. Indeed, oxidized titanium implant surfaces have been shown to have superior performance when compared with turned implant surfaces in pre-clinical (Botticelli et al. 2005, Sul et al. 2006, Salata et al. 2007) and clinical settings (Ivanoff et al. 2003). Improved osseointegration have been attributed to an increased titanium oxide layer, which provides greater surface porosity and consequently greater surface area. In the present study, the oxidized titanium implant surface was coated with PC, which likely somewhat changed the characteristics of the implants. The immediate impact of the PC coating on the surface topography of the implants was not evaluated directly; however, the results may indicate that the influence of the PC coating is probably more associated with the electrical charge than any major impact on implant surface characteristics.

In the present study, the whole specimen was used for the histometric evaluation. In contrast, some authors have used information pertaining only to the three best consecutive treads of the implant (Franke Stenport et al. 2003). This approach proved to be very difficult in the tibia due to narrow cortical bone, and in the femur it would not allow for an overall assessment of the therapies. Nevertheless, the present histometric analysis was sufficiently discriminatory to show differences between the experimental groups, even though they were not all statistically significant. Moreover, histometric measurements were in accordance with the removal torque analysis, further indicating the appropriateness of the methodology used.

In conclusion, the histometric and biomechanical analyses suggest that PC coating may influence the biological processes and ultimately osseointegration of endosseous implants. Apparently, incorporation of cationic charges

may reverse or compensate for this scenario. Nevertheless, both PC coatings exhibited clinically acceptable osseointegration. In perspective, PC technology appears to be a viable candidate delivery system for agents in support of local bone formation at oral implant surfaces.

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Clinical Relevance

Scientific rationale for the study: Compounds considered for drug delivery from oral implant surfaces in support of local bone formation might themselves influence osseointegration. This study evaluated local bone formation and osseointegration at implants coated with a PC polymer known to enhance the biocompatibility of medical devices and to serve as a drug delivery system. Uncoated oxidized titanium endosseous implants served as control.

Principal findings: Using an established rabbit model, PC-coated implants exhibited significantly lower osseointegration and removal torque values compared with control ($p < 0.05$). The reduced osseointegration was reversed by positively charging the PC coating. Nevertheless, both coatings exhibited clinically acceptable osseointegration.

Practical implications: PC technology appears to be a viable candidate delivery system for agents in support of local bone formation at endosseous implant surfaces.