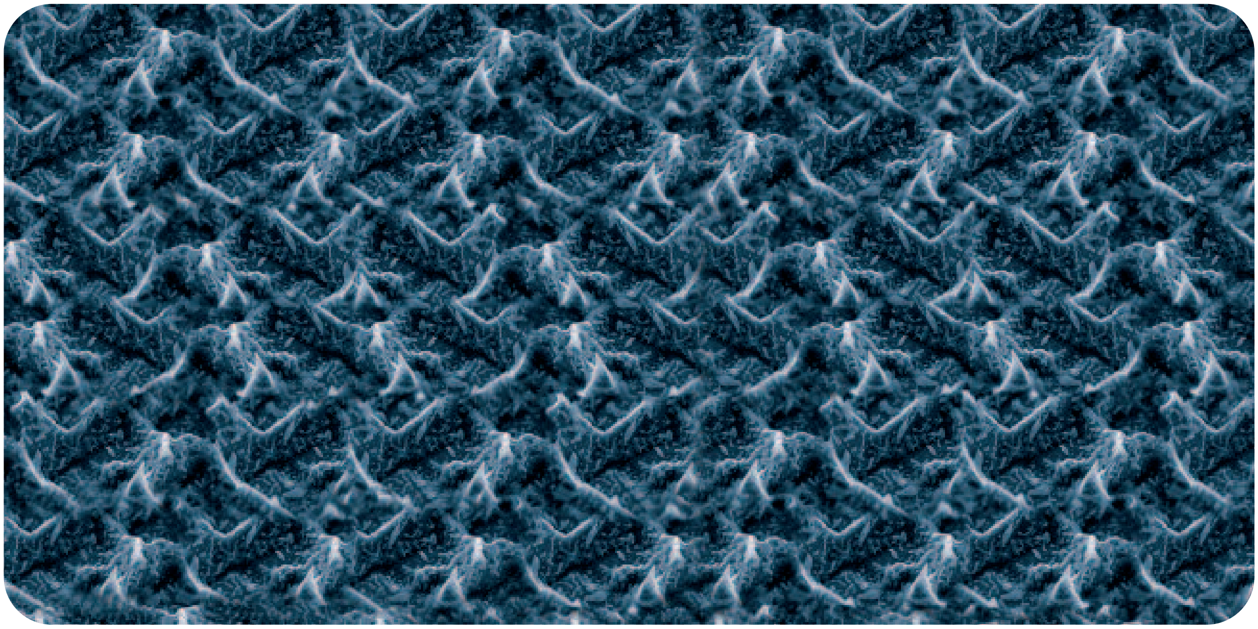


Research Dossier

The NanoTite™ Implant

NanoTite Certain® Implant   NanoTite PREVAIL® Implant

NanoTite™ IMPLANT SYSTEM

Steve Schiess

We are proud to present in this dossier a body of data documenting the performance of the NanoTite™ Implant.

For more than ten years we have utilized the dual-acid-etched OSSEOTITE® Surface treatment to improve our implant's success, and more importantly change the way our customers are able to treat their patients. Before the launch of the OSSEOTITE Implant, a two-stage implant placement and restoration procedure requiring a four to six month submerged healing protocol was the standard approach. The clinical and preclinical studies conducted and published on the OSSEOTITE Implant provided insights as to the nature of how dental implants heal and function in general. Clinical investigators found that "early loading" in which implants were placed in a single-stage approach and put into function at eight weeks was just as successful as for delayed-loading cases. The growing demand by patients and clinicians for immediately loaded restorations suggested that additional surface improvements might be of clinical benefit.

In early 2003, research efforts at the UCLA Weintraub Center brought to our attention a nano-technology that we have used to further enhance the OSSEOTITE Surface. Throughout the past four years, the combined efforts of researchers and clinicians around the globe have allowed for the accumulation of data to help characterize the effects of the new surface. Contributions from researchers at the Universities of Toronto, UCLA, D'Anunzio in Chieti, Italy and elsewhere provided the product development group at BIOMET ***3i*** *the means to validate this technology and launch it into commercial introduction as a new dental implant known as the NanoTite™ Implant.*

These NanoTite Implant results are compelling and as much as we are interested in the nature of these results, we are more concerned with keeping a focus on the benefits we believe can be appreciated by patients and clinicians. By increasing the early fixation of the implant in the osteotomy, we are looking to show that a greater patient sample can be qualified for immediate or early loading cases, that the overall number of unexplainable failures can be greatly reduced and that otherwise challenging cases may be made more routine. We hope you find the studies and results presented herein of interest and helpful for considering how this new technology may benefit patient care.

Steve Schiess, President
BIOMET ***3i***

Table Of Contents

Dissolution Of Discrete Calcium Phosphate Crystals From Candidate Ti-based Implant Surfaces

Padina Pezeshki, Stanley Lugowski, John E. Davies, Faculty of Dentistry, Institute of Biomaterials and Biomedical Engineering, Faculty of Engineering, University of Toronto

Canadian Biomaterials Society

25th Annual Meeting (May 26–28, 2006, Calgary, Alberta, Canada)

Introduction

Plasma-spraying of dental and orthopedic implants with calcium phosphate (CaP) was introduced in the mid-1980s as a means of accelerating early peri-implant bone healing and rendering the implant surface bone bonding [1]. While some success has been, and continues to be, achieved clinically; problems have also been identified due to disintegration and delamination of such relatively thick (approx. 50 micron) coatings. The latter, due to the high temperature plasma-spray method, results in a heterogeneous CaP coating composition comprising several possible CaP phases of differing solubilities. Thus, the solubility of these and other coatings achieved through biomimetic strategies or sol-gel technology has been a subject of considerable study and different fabrication methods have aimed to modify the properties that influence the CaP dissolution rate such as phase, particle size, surface area, and porosity [2,3]. Recently, a new means of modifying metallic surfaces with CaP has been developed that comprises the deposition of discrete crystals of CaP from solution onto the metal oxide surface. In suspension the CaP crystals are of the order of 20-100nms, which can be deposited on the surface as a function of immersion time. Our current study was designed to quantify the amount and dissolution kinetics of these discrete CaP crystals from Ti6Al4V alloy dental implant surfaces and compare their behavior with commercially-available plasma sprayed CaP coated implants of a similar size. Since activated macrophages and osteoclasts can locally reduce the extracellular pH to four, we chose an investigational pH range of 4-7 for our experiments.

Materials And Methods

Two Ti6Al4V implant types were employed. The DCD-treated implants were IOSS615 (6mm diameter x 15mm length) and plasma sprayed CaP implants were HT 613 (6mm diameter x 13mm length): both supplied by BIOMET ***3i*** in Palm Beach Gardens, Florida. Experiments were carried out to (i) measure the total amount of Ca on the surface of the implants and (ii) the amount of Ca released in pH-specific solutions. In order to measure the traces of Ca, all experimental equipment was initially cleaned to clear Ca contamination. For determination of total amount of Ca on the surfaces, each DCD-treated implant was immersed in 10ml of 1 M Ultrex Grade HCl (pH

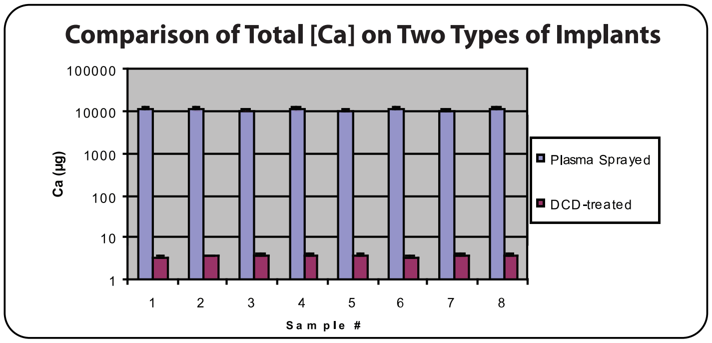


Figure 1: Comparison of total [Ca] on plasma sprayed and DCD-treated implants

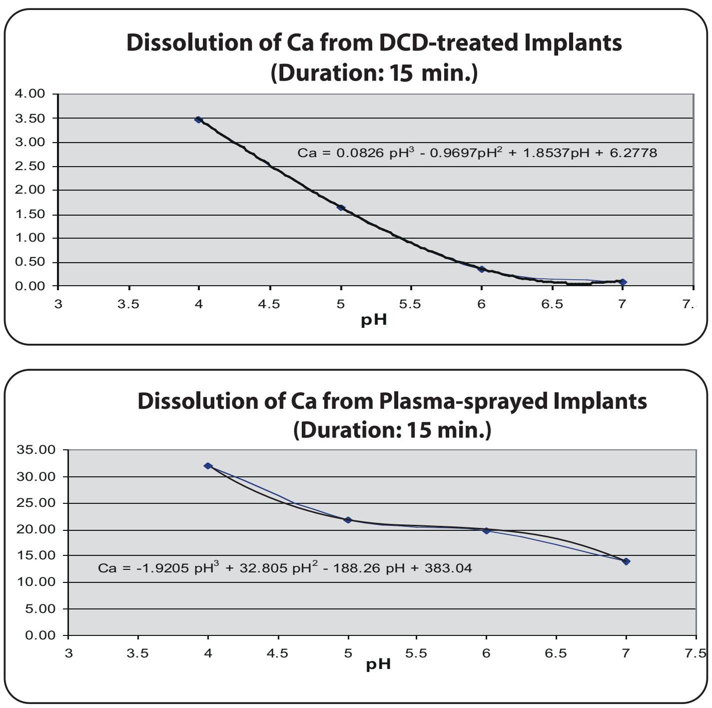
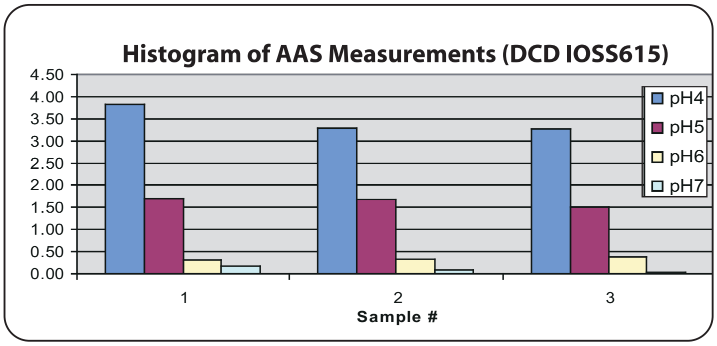


Figure 2: Comparison of different implants' dissolution response

0, by JT Baker, Phillipsburg, NJ) for 15 minutes and each plasma sprayed sample for 16 hrs, (n=8). For the second part of the experiment, samples were placed in 10ml of saline solution with fixed pH of 4, 5, 6 or 7 (by adding clean HCl or NaOH in a drop-wise fashion) for 15 minutes (n=3). The samples were then removed and the total Ca in the remaining solution was measured using atomic absorption spectrophotometry. Furthermore, the morphology of the surfaces was qualitatively analyzed using field emission scanning electron microscopy (FESEM).



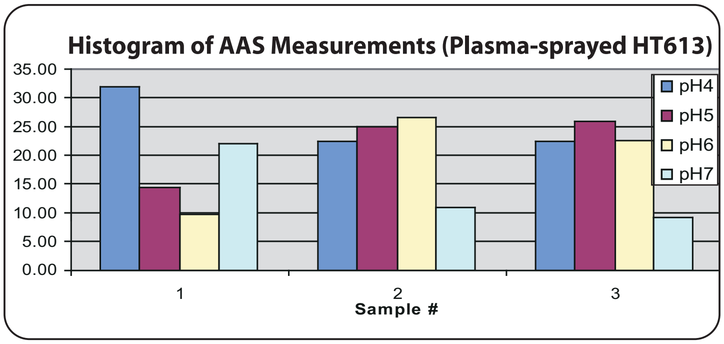


Figure 3: Comparison of distribution of data for the two implant types

Results And Discussion

The results revealed a reproducible difference of three orders of magnitude less in the amount of calcium removed from DCD-treated implants when compared to plasma-sprayed implants (3.81 vs. 11551.29 µg respectively) (Figure 1). Moreover, the dissolution of Ca in a specified time as a function of pH demonstrated a clear trend between the measured Ca and the pH of the solution (Figure 2). This is relevant to initial steps of biological healing, where activated macrophages, which may randomly contact the implant surface, could reduce the local pH to four. Moreover, as the body pH proceeds to its natural pH of 7.4, the dissolution of CaP from DCD implants is almost zero, while dissolution does occur from multi-phase plasma-sprayed implants. Finally, the pH-dependent dissolution of the two implant types were compared and a variation was observed (Figure 3), which demonstrated a more consistent CaP phase for the DCD samples and multi-phase CaP surface for the plasma sprayed samples.

Conclusion

DCD-treatment provides implants with a more consistent and stable phase of CaP as well as lower amounts of CaP that would not invoke the known problems associated with dissolution of CaP from plasma-sprayed coatings.

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1. Sun *et al.,* J Biomed Mater Res. 2001;58(5):570-92
2. Yang *et al.*, J Biomaterials 2005;26;327-337.
3. Zeng *et al.,* J Biomaterials 1999;20(5):443-351

Surface Area Increase Due To Discrete-Crystalline-Deposition Of Nanometer-scale CaP Crystals

Zach Suttin, Prabhu Gubbi, BIOMET ***3i****, Palm Beach Gardens, Florida, USA*

European Association For Osseointegration

15th Annual Meeting (October 5–7, 2006, Zurich, Switzerland)

Introduction

This study estimates the increase in surface area (SA) due to the deposition of nano-scale calcium phosphate (CaP) crystals onto a dual-acid-etched (DAE) implant surface.

Materials And Methods

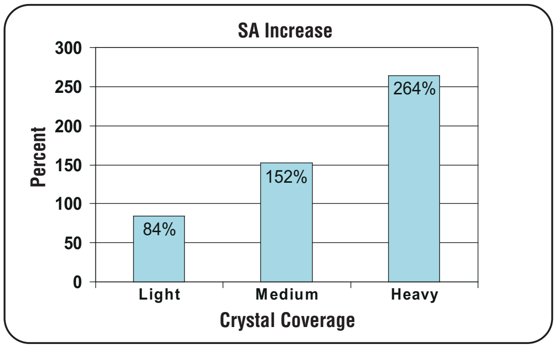
Atomic Force Microscopy (AFM) is used to quantify surface measurement parameters of surfaces with nanometer topographical characteristics. In addition to the AFM data currently being generated, this study uses theoretical 3-D modeling to estimate the SA increase due to the deposition of nano-CaP crystals onto a DAE surface. The size, shape and distribution of the nano-CaP crystals were based on the dimensions obtained from FESEM (JEOL Model 6700F) images. The crystals were modeled as ellipsoids with sizes ranging from 20-80nm on the long axis and 10-39nm on the short axis. Based on the FESEM imaging, the distributions of crystal coverage considered for the analysis were classified as light (25-30%), medium (55-60%) and heavy (65-70%).

Results And Discussion

The calculated estimates for SA increase due to nano-CaP deposition were 84%, 152% and 264% for the light, medium and heavy crystal coverage, respectively. Furthermore, compared to a machined surface, the DAE treatment increases the implant SA > 50% (data on file), and it was estimated that the increase in implant SA with the addition of nano-CaP onto the DAE surface ranges from 176% to 446%.

Conclusion

Deposition of nano-scale CaP crystals over a micron-scale DAE surface significantly increases the overall SA and topographical complexity.



Roughness Characterization Of Surface With Discrete-Crystalline-Deposition Of Nanometer-scale CaP Crystals

Prabhu Gubbi, Zach Suttin, Alexis Goolik, BIOMET ***3i****, Palm Beach Gardens, Florida, USA*

Academy Of Osseointegration

22nd Annual Meeting (March 8-10, 2007, San Antonio, Texas)

Introduction

The objective of this study was to characterize the surface roughness of polished titanium disks with nanometer-scale calcium phosphate (CaP) crystals deposited by a new proprietary surface treatment called discrete-crystalline-deposition (DCD).

Materials And Methods

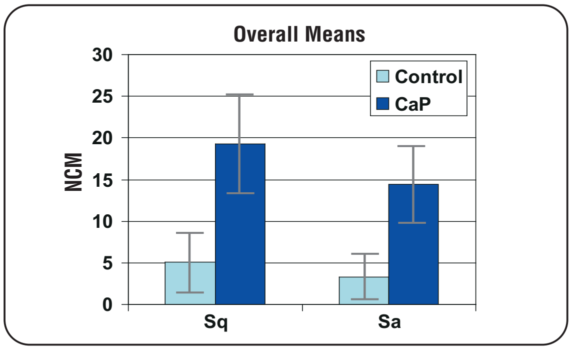
Ti (Ti-6Al-4V-ELI) disks, 20mm in diameter and 1.5mm in thickness, were machined and polished on one side to a mirror finish (Control group). A group of polished disks were deposited with nano-scale CaP crystals using the DCD process (CaP group). Atomic Force Microscopy (AFM), widely employed to quantify surface measurement parameters of surfaces with nanometer topographical characteristics, was used to obtain surface maps. Using AFM (Model MMAFM-2, Digital Instruments) in tapping mode, two disks from each group were analyzed with various spot sizes. The data were post-processed using a 3x3 low filter, with background subtraction, and line by line averaging with a 3x3 degree polynomial. The key roughness parameters obtained were Sq (root mean square variation over the surface) and Sa (absolute mean height deviation).

Results And Discussion

The calculated overall means for the Control group (N = 20 data points) were Sq = 5.04nm ± 3.62nm and Sa = 3.29nm ± 2.37nm. For the CaP group (N = 18 data points), the corresponding values were Sq = 19.3nm ± 6.4nm and Sa = 14.8nm ± 5.1nm.

Conclusion

The surface roughness characterization using AFM suggests that the deposition of nanometer-scale CaP crystals over a polished surface substantially increases the topographical complexity.



Adhesion Shear Strength Of Nanometer-scale CaP Crystals Applied By Discrete-Crystalline-Deposition

Zach Suttin, Prabhu Gubbi, BIOMET ***3i****, Palm Beach Gardens, Florida, USA*

European Association For Osseointegration

15th Annual Meeting (October 5–7, 2006, Zurich, Switzerland)

Introduction

In this study, the adhesion shear strength of nano-scale calcium phosphate (CaP) crystals deposited onto dual-acid-etched (DAE) surfaces was evaluated using Atomic Force Microscopy (AFM) and was compared to the shear stress at the implant-bone interface during implant placement.

Materials And Methods

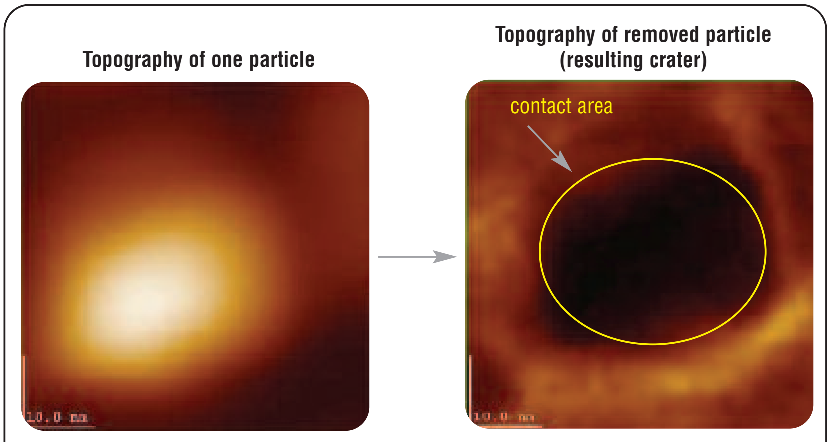
CaP crystals deposited onto CP Ti (n=30) and Ti Alloy (n=30) DAE surfaces were dislodged using contact mode AFM (Model MMAFM-2, Digital Instruments). The adhesion shear strength of each crystal-surface bond was calculated as the ratio of the maximum shear force supported by the crystal before separation to the contact area between the crystal and the surface. In a separate experiment, the torque required to place 6mm diameter implants into simulated bone (polyurethane foam of density 640kg/m^3) was measured (n=30) with a Mark-10 digital torque indicator. The average and maximum shear stresses generated at the implant-bone interface were calculated from the implant insertion torque values. For additional details, see pages 7-10.

Results And Discussion

The average crystal-surface adhesion shear strength from AFM analysis was 1.75GPa for CP Ti and 1.52GPa for Ti Alloy. The maximum torque for implant placement was 17N-Cm, which resulted in an average shear stress of 3.61x10^{-4}GPa at the implant-bone interface. The maximum shear stress, occurring at the fore threads in the apical zone, was 5.14x10^{-1}GPa.

Conclusion

The average crystal-surface adhesion shear strength was three orders of magnitude greater than the average implant-bone interface shear stress. The results indicate that the nano-scale CaP crystals deposited onto either CP Ti or Ti Alloy DAE surfaces will not dislodge during implant placement.



Shear Strength Analysis Using Contact-mode Atomic Force Microscopy (AFM)

Determination Of CaP Crystal Shear Strength Using Contact-Mode Atomic Force Microscopy (AFM)

Gajendra Shekhawat, PhD - Research Assistant Professor, Northwestern University Institute of Nanotechnology, Northwestern University, Zach Suttin , BIOMET ***3i****, Palm Beach Gardens, Florida, USA*

Bench Testing

Abstract

In a new surface treatment process, discrete nanometer-scale calcium phosphate (CaP) crystals are bonded to an OSSEOTITE® Implant surface. The strength of the bond between the implant surface and the CaP crystals can be used as an indicator of the likelihood of the discrete crystals becoming dislodged during implant placement. The objective of this experiment was to determine the shear strength of these crystals deposited on an OSSEOTITE Implant surface using contact-mode AFM analysis.

Background

Contact-mode AFM analysis can be used to determine the adhesion strength (e.g., shear strength) of a discrete nanometer-scale particle (such as a CaP crystal) bonded to a surface. This analysis uses a nanometer length scale Silica Nitride (SiN) calibrated beam with a diamond coated probe (or tip). The probe is displacement-controlled and the equivalent force is calculated using beam mechanics. The contact-mode AFM analysis is initiated by placing the probe on a discrete particle. The beam displacement is slowly increased until the displacement load dislodges the particle. For shear strength and compressive strength analysis, the probe is moved tangential and normal to the surface on which the crystal is adhered to. Figure 1 depicts an example shear strength contact-mode AFM assay.

The results can be used to determine the shear strength of the crystal. The shear strength **(τ_S)** is a function of:

- Force **(F)**
- Contact area **(A_c)**

The shear strength can be equated as:

$$\tau_S = \frac{F}{A_c} \quad \text{........equation (1)}$$

The results for the above experiment shown in (Figure 1) can be interpreted as follows:

Contact Area **(A_c)** – Since the particle appears to be approximately 20nm in diameter (relative to the scale), the contact area between the particle and the surface can, therefore, be reasonably estimated to be between $7.85e^{-17}m^2$ and $3.14e^{-16}m^2$ (based on a contact radius of 5nm to 10nm).

Shear Force **(F)** – A 150nN shear force was required to dislodge the particle.

Shear Strength **(τ_S)** – Using equation (1), the shear strength of the particle can be estimated to be between $4.7x10^{-1}$GPa and 1.91GPa. The range in shear strength is due to the estimated range of the contact area as described above.

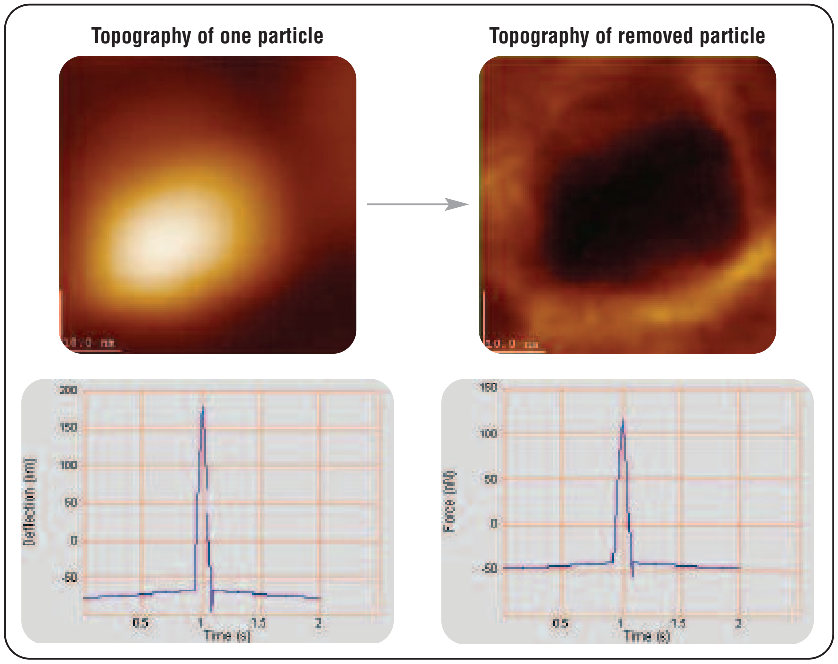


Figure 1: Shear strength contact-mode AFM assay

Materials

- Three (3) nanometer-scale CaP crystal processed CP Ti OSSEOTITE® 20mm disks (Control #4543 / Batch #115-72-B)
- Three (3) nanometer-scale CaP crystal processed Ti-Alloy OSSEOTITE 20mm disks (Control #4544 / Batch #115-72-B)
- Contact-mode AFM (Multimode PicoForce Scanning Probe Microscope)

Methods

- Shear thirty (30) crystals from the CP Ti disks using contact-mode AFM. Acquire the shear force and contact area values for each data point.
- Shear thirty (30) crystals from the Ti-Alloy disks contact-mode AFM. Acquire the shear force and contact area values for each data point.

The experimental analysis was conducted by Dr. Gajendra Shekhawat at Northwestern University's Atomic and Nanoscale Characterization Experimental Center (NUANCE).

Results

Table 1 lists the results for the contact-mode AFM analysis. The force values, which are a function of beam displacement, are output by the AFM software. The contact area values are measured with the AFM following the removal of each crystal. The shear strength was calculated using equation (1).

The mean, standard deviation, low and high shear strength values for the nanometer-scale CaP crystals bonded to both types of OSSEOTITE substrates are shown in Table 2. The crystals on the CP Ti substrate had an average strength 15% higher than the crystals on the Ti Alloy substrate.

Although the main objective of this assay was to determine the shear strength of the nanometer size CaP crystals, an abbreviated compressive strength assay was subsequently conducted. The purpose of this secondary experiment was to verify that the compressive strength of the crystals exceeded the shear strength of the crystals bonded to the OSSEOTITE Surface. Four crystals, two from each substrate type, were compressively loaded with the probe until they fractured. The compressive force values required to fracture the crystals ranged from 3.8μN to 6.60×10^{2}μN. The 3.8μN value is more than one order of magnitude greater than the shear force values required to shear the crystals from the substrate.

Table 1: AFM Analysis Results

	Ti Alloy			CP Ti		
Crystal No.	Force (nN)	Area (nm^2)	Shear Strength (GPa)	Force (nN)	Area (nm^2)	Shear Strength (GPa)
1	128	137.2	0.93	241	114.3	2.11
2	166	162.6	1.02	242	141.4	1.71
3	228	128.2	1.78	236	137.6	1.72
4	167	143.5	1.16	243	142.3	1.71
5	188	141.6	1.33	241	167.6	1.44
6	232	118.4	1.96	242	171.4	1.41
7	187	118.6	1.58	238	154.6	1.54
8	202	108.4	1.86	240	124.7	1.92
9	224	141.7	1.58	231	148.9	1.55
10	230	148.4	1.55	242	179.4	1.35
11	222	146.6	1.51	243	119.6	2.03
12	207	133.5	1.55	236	122.4	1.93
13	206	145.5	1.42	241	113.4	2.13
14	222	115.6	1.92	237	121.4	1.95
15	201	129.6	1.55	242	136.4	1.77
16	191	123.3	1.55	252	138.5	1.82
17	218	112.7	1.93	237	142.2	1.67
18	188	118.2	1.59	256	120.4	2.13
19	187	117.2	1.60	254	175.4	1.45
20	193	113.4	1.70	253	172.2	1.47
21	175	132.6	1.32	296	117.4	2.52
22	200	115.6	1.73	258	126.4	2.04
23	184	106.6	1.73	269	132.4	2.03
24	196	114.7	1.71	241	129.6	1.86
25	209	129.5	1.61	222	132.7	1.67
26	219	149.5	1.46	249	126.4	1.97
27	232	131.2	1.77	221	156.4	1.41
28	204	166.8	1.22	219	144	1.52
29	222	225	0.99	238	162	1.47
30	236	258.8	0.91	279	242	1.15

Table 2: Shear Strength Statistics From Table 1

	Shear Strength (GPa)			
Substrate	Average	Standard Deviation	Low	High
Ti Alloy	1.52	0.29	0.91	1.96
CP Ti	1.75	0.3	1.15	2.52

Qualitative Evaluation Of Crystal Adhesion During Implant Placement In Simulated Bone Medium

Zach Suttin, BIOMET ***3i***, *Palm Beach Gardens, Florida, USA*

Bench Testing

Abstract

The implant-bone interface experiences shear stress during implant placement. The objective of this test was to qualitatively measure whether or not nanometer-scale CaP crystals discretely bonded to OSSEOTITE® Implants would dislodge during placement and removal in a simulated bone material. Ti- Alloy and CP Ti OSSEOTITE Implants with discretely bonded nanometer-scale CaP crystals were placed in and removed from a simulated bone medium. The implants were then imaged with a field emission scanning electron microscope (FE SEM) to determine if the nanometer-scale CaP crystals had become dislodged. Based on the imaging results, it is evident that the nanometer-scale CaP crystals did not become dislodged during implant placement and removal.

Materials

- Six (6) nanometer-scale CaP crystal processed Ti-Alloy 4mm TG FOSS CaP implants (Control #P-84 / Batch #115-68-B)
- Six (6) nanometer-scale CaP crystal processed CP Ti 4mm TG FOSS CaP Implants (Control #P-83 / Batch #115-68-B)
- 3740 LAST-A-FOAM®
- Medium stiffness toothbrush

Methods

The two groups of six (6) implants were used in the experiment as follows:

1) Control
2) Brush
3) Polymer
4) Polymer + Brush (1)
5) Polymer + Brush (2)
6) Polymer + Brush (3)

Two of the implants in each group (1 & 2) were not screwed into the simulated bone medium. The number (1) implant was used as a control and the number (2) implant was used to determine if the toothbrush alone would remove the CaP crystals. Four of the implants from each group (3, 4, 5 & 6) were screwed into and removed from the simulated bone medium. Implants (4), (5) and (6) were then brushed to try and remove the simulated bone medium (polymeric material). The number (3) implant was not brushed off so it could be used for comparison to the other implants.

STEP 1: Eight (8) blind holes in the 3740 LAST-A-FOAM were drilled using a 3.25mm twist drill.

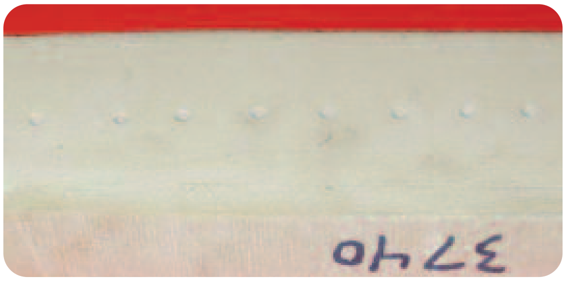


Figure 1: 3740 LAST-A-FOAM with eight (8) 3.25mm blind holes

STEP 2: Four (4) implants from each group were screwed into one of the blind holes and then removed.

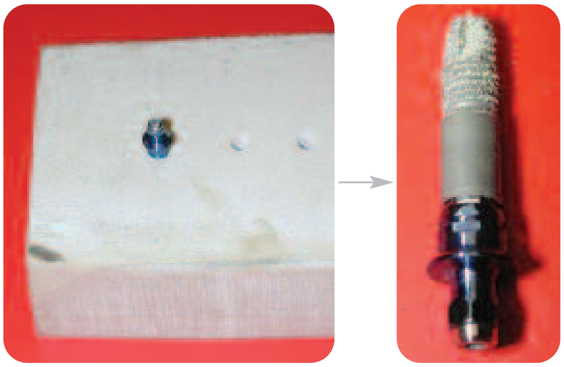


Figure 2: An implant placed in and then removed from a blind hole

STEP 3: Three (3) of the four (4) implants from each group which were screwed into the bone were lightly brushed to remove the polymeric debris.

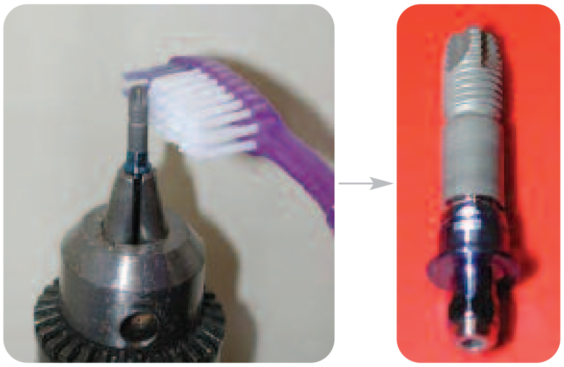


Figure 3: An implant placed in a fixture for brushing and then removed

STEP 4: The implants were then imaged using a FESEM at the apical (in red) and coronal (in green) aspects. The images were taken on surfaces at a 45 degree angle relative to the electron beam direction. The FESEM imaging was performed by Materials Analytical Services, Inc. in Raleigh, NC.

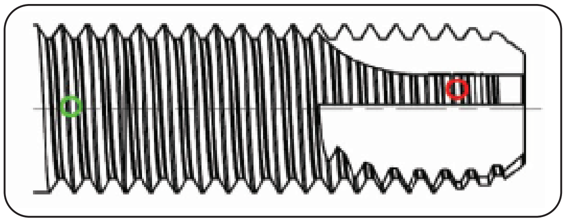
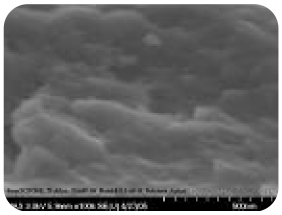


Figure 4: Location of acquired FESEM images

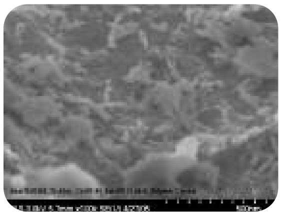
Results

Below is an example of a 100kX image for the apical and coronal aspects of one of the twelve (12) implants:

Ti-Alloy + Polymer



Apical



Coronal

Observations

- The “control” implant images show nanometer-scale CaP crystals in both the apical and coronal aspects.
- The “brush” implant images show nanometer-scale CaP crystals in both the apical and coronal aspects. The brushing, therefore, did not remove the nanometer-scale CaP crystals.
- The “polymer” implant images show nanometer-scale CaP crystals at the coronal aspect and not at the apical aspect. The polymer, therefore, agglomerated at the apical aspect during implant placement (meaning that the nanometer-scale CaP crystals sheared/collected the polymer). The nanometer-scale CaP crystals in the coronal aspect did not shear the polymeric material as much as in the apical aspect since the threads in the coronal aspect are just following the geometry created by the apical threads versus shearing the simulated bone medium.
- The “polymer + brush” implant images were similar to the “polymer” implant images. One difference is that in the “CP Ti polymer + brush (1)” images the nanometer-scale CaP crystals in both the apical and coronal aspects can be seen. It was anticipated that this would be the case for all “polymer + brush” implants, but it turned out to be difficult to remove the polymer with the brush in most instances. Another difference is that polymeric material can be seen in the “Ti-Alloy + Polymer + Brush (1)” coronal image. So in this one case some polymeric material agglomerated in the coronal aspect of the implant (as opposed to just the apical aspect) as well.

Conclusion

This assay indicates qualitatively that nanometer-scale CaP crystals discretely bonded to OSSEOTITE® Implant surfaces will not become dislodged during implant placement. Although the nanometer-scale CaP crystals could not be seen on the apical aspect post screw in/out, it is reasonable to assume that the crystals have been covered by the polymer (instead of being sheared off by the polymer) in this area. This argument is supported by considering the image of the apical aspect from the “CP Ti polymer + brush (1)” implant.

*Discrete Calcium Phosphate Nanocrystals Render Titanium Surfaces Bone Bonding**

Vanessa C. Mendes, John E. Davies, Institute of Biomaterials and Biomedical Engineering, Faculty of Dentistry, University of Toronto, Ontario

Canadian Biomaterials Society

25th Annual Meeting (May 26–28, 2006, Calgary, Alberta, Canada)

Introduction

The surfaces of titanium dental implants have evolved with a variety of microtextures that have been shown to accelerate early bone healing and increase implant stability [1,2]. Specifically, microtextured surfaces of either metallic or calcium phosphate (CaP) implants have been shown to improve healing by upregulation of platelet activation [3,4] and increasing fibrin retention to the implant surface; which are elements necessary to signal, and provide a transient biological matrix for, osteogenic cell migration to the implant surface that results in contact osteogenesis [5]. An additional benefit of CaP coatings – usually ≥ 50 microns thick – is that they have been shown to not only accelerate early healing but also permit bone bonding to their surfaces. The latter is a benefit unobtainable with metallic surfaces [6]. Nevertheless, CaP plasma-sprayed implants also have demonstrated clinical problems due to delamination and resultant particulate formation in vivo which have led to inflammatory responses and implant failure under loading. For this reason, particularly in the dental implant field, CaP-coated surfaces have been largely replaced by microtextured metallic surfaces.

Recently, it has been shown that it is possible to modify an already clinically successful microtextured metallic surface by the deposition of discrete nano-crystals of CaP. These deposited crystals have little effect on the micron-scale texture of the metallic surface, but do superimpose upon it a nano-scale topographical complexity. Indeed, we show elsewhere at this conference that such discrete CaP crystalline deposits (DCD) can significantly accelerate osteoconduction. The purpose of the present study was to design an experiment to ask the question: Can such CaP/DCD render a metallic implant surface bone-bonding? To address the question, we designed custom implants to measure the strength of attachment of bone to a candidate implant surface.

Materials And Methods

Custom designed rectangular implants, 6x4x1.5mm, were fabricated from either commercially pure (“cp”) or titanium alloy (Ti6Al4V or “alloy”). Each implant had a central hole down the long axis to enable suture fixation at surgery. All implants were dual-acid-etched (DAE) using either H_2SO_4/HCl or HCl/HF for cp and alloy implants respectively. Half of the cp and alloy implants were modified by the CaP/DCD (nominal crystal size 20nm; surface coverage approx. 50%; modified particulate sol-gel deposition method). Thus, a total of four groups: cp, cpDCD, alloy, and alloyDCD were generated. Forty eight implants (12 per group) were placed antero-posteriorly into the distal metaphyses of both femora of male Wistar rats for nine days. The femora of the sacrificed animals were trimmed to the width of the implant and placed in sucrose buffer. The resulting samples consisted of two cortical arches of bone attached to each implant (n=96). For each sample, nylon lines were passed through the marrow spaces between the implant and each cortical arch and the implant was secured in a vice attached to an Instron™ Testing Machine (model 8501) (Figure 1). Each nylon line was then attached to the Instron Frame, displaced at a crosshead speed of 30mm/min, and the force to rupture the sample was recorded. Thus, for each implant, two force/displacement results were generated, one for each femoral arch (medial or lateral). Scanning electron microscopy (SEM) was used as a qualitative method to analyze the bone/implant interface following the detachment assay.

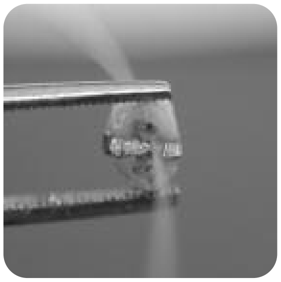


Figure 1: Preparation of sample for the tensile test.

Results And Discussion

The post-operative period was uneventful for all rats, except one, which had problems load-bearing and was excluded from the study. One sample was compromised while being positioned in the Instron Machine. Thirty two arches (16 cp, 2 cpDCD, 12 alloy and 2 alloyDCD) were insufficiently attached to the surface of their implant to withstand sample handling. These data were included in the study. The resulting 63 samples were tested as described above. DCD implant surfaces, either cp or alloy, had statistically significantly greater average values of detachment force (cp 7.08N and alloy 11.30N) than controls (cp 0.60N and alloy 1.90N) (Figure 2). Furthermore, DAE alloy surfaces exhibited

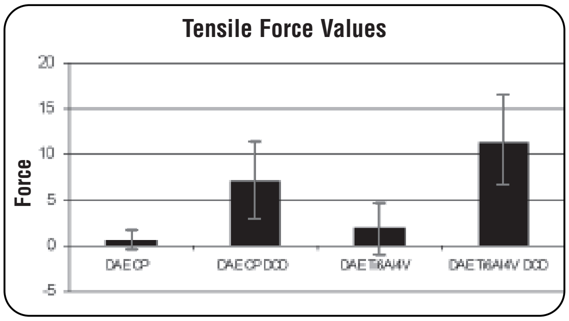


Figure 2: Tensile force values for all four groups.

*Bone Bonding™ is the interlocking of bone with the implant surface.

statistically significant higher detachment force results than DAE cp. This was expected and could be explained by the enhanced microtopographical complexity of the alloy surface as compared to the cp surface.

The bone-bonding phenomenon was demonstrated in this study by visual inspection of the samples (Figure 3) and SEM. In samples with high "detachment" forces, the bone arches had fractured while the bone in contact with the implant surface was not detached. No such bone-bonding was observed in the DAE samples.

Figure 3: Bone-bonding phenomenon.

Conclusion

DAE implant surfaces can be improved and rendered bone-bonding by nano-structured CaP surface modification; and DAE alloy demonstrates greater bone attachment than DAE cp titanium.

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Acknowledgements: CIHR Fellowship (VCM), Grants from ORDCF and BIOMET ***3i***, Palm Beach Gardens, Florida (JED)

Discrete Calcium Phosphate Nanocrystals Enhance Osteoconduction On Titanium-based Implant Surfaces

Vanessa C. Mendes, John E. Davies, Institute of Biomaterials and Biomedical Engineering, Faculty of Dentistry, University of Toronto, Ontario

Canadian Biomaterials Society

25th Annual Meeting

(May 26–28, 2006, Calgary, Alberta, Canada)

Introduction

Contact osteogenesis, or the apparent growth of bone on (or along) an implant surface, is the result of both osteoconduction, which we have defined as the "recruitment and migration of osteogenic cells", and the subsequent secretory activities of these migrated cells which results in the elaborated bone matrix. The surface microtopography of implants has been demonstrated to influence biological response in the peri-implant compartment and, specifically, to enhance early peri-implant healing and promote increased bone-implant contact when compared to smooth surfaces.[1,2,3] These mechanisms have now been thoroughly documented.[4,5] We have previously described a bone-ingrowth chamber model to quantitatively measure osteoconduction, normally referred to as Bone Implant Contact (BIC).[2] However, without further refinements of the model, we have not, until now, employed this method to compare osteoconduction on metallic surfaces of essentially similar microtopography. We describe herein, the detailed design of, and refinements to, this miniature bone ingrowth chamber model; the processing techniques we have developed to derive histological data from multiple samples in parallel; the block face preparation and back-scattered electron imaging techniques we employ to derive multiple planes of examination from each multiple sample group; and the means of quantitatively analyzing the experimental results.

Our results show that etched titanium alloy is more osteoconductive than commercially pure titanium. When modified by nano-scale deposits of calcium phosphate crystals, osteoconduction on both metals is further significantly increased.

Materials And Methods

Custom designed T-shaped implants ("Tplants"), 5 x 3 x 2mm, were fabricated by BIOMET ***3i*** in Palm Beach Gardens, Florida, USA, from either commercially pure ("cp") or titanium alloy (Ti6Al4V or "alloy"). The stem of the "T" is hollow with a cavity 3x2x1mm into which bone could grow following implantation (Figure 1). The Tplants are constructed in modular parts so that their inner walls can be surface modified before assembly. On one external surface, a notch was laser-etched in an angle of 45°, to enable calculation of the height of each cross section of the chamber during sample analysis. All implants were dual-acid-etched (DAE) using either H_2SO_4/HCl or HCl/HF for cp and alloy implants respectively. Half of the cp and alloy implants were modified by the CaP/DCD (nominal crystal size 20nm; surface coverage approx. 50%; modified particulate sol-gel deposition method). Thus, a total of four groups: cp, cpDCD, alloy and alloyDCD were generated. Four groups of 25 Tplants of each experimental group (total=100), were placed antero-posteriorly into the distal metaphyses of both femora of male Wistar rats for nine days (Figure 2). After harvesting, individual samples (Figure 3) were mounted in groups of 10 on custom plate holders (Figure 4) and resin embedded for block-face microscopy (Figure 5). The block surface was repeatedly ground (automated polishing machine, EcoMet 3000 & AutoMet 200 Power Head, Buehler, IL, USA) to produce back-scattered electron images (BSEI), following platinum sputter coating, of different planes of the implant chamber (Figures 6 and 7). Quantitative analysis of BIC was performed with the software Sigma Scan Pro 4 (SPSS Inc.) on >450 micrographs. Single and multiple analysis of variance (ANOVA) were applied to bone contact measurements as a function of metal (cp vs. alloy) and modification with CaP. All statistical analysis were conducted using JMP v5.0.1 software (SAS Institute, Inc., Cary, NC). Statistical significance was considered at $p < 0.05$ and a Tukey-Kramer HSD post hoc analysis was applied to mean comparisons where indicated by an overall statistical influence.

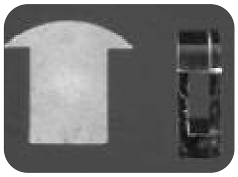

Figure 1

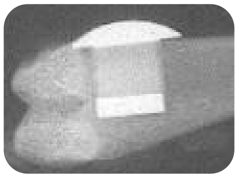

Figure 2

Figure 3

Figure 4

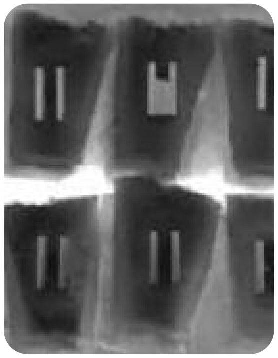

Figure 5

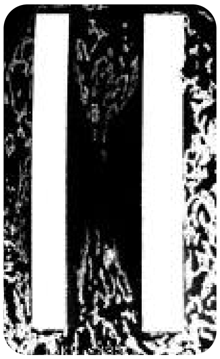

Figure 6

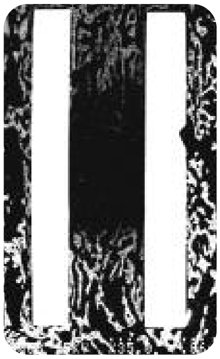

Figure 7

Results And Discussion

The post-operative period was uneventful. In a total of 100 femurs, there were 3 fractures. Those samples were excluded from the study. Our initial analysis indicated osteoconduction in all groups. Osteoconduction was identified by bone growth along the walls of the implant. Osteoconduction on both DAE-DCD groups (cpTi and Ti6Al4V) was significantly enhanced in all levels of analysis. This was statistically significant when compared to the results of DAE groups in all levels of analysis (independent measurements and aggregate measurements per layer and per implant). Interestingly, when the metals (cpTi or Ti6Al4V) were isolated, it was demonstrated that there was no statistical difference between both metals in an analysis of aggregate measurements per implant. However, statistically significant differences were verified, with respect to increased values of osteoconduction on Ti6Al4V, in an analysis of either aggregate measurements per layer or independent bone contact measurements.

This study has also shown, in a consistent manner, a variation of the amount of bone-implant contact dependent on anatomical location. The proximal side of the chamber had significantly higher bone-implant contact than the distal side. It is suggested that the direction of the vascular supply flow (from proximal to distal) in the rat femur would have been responsible for that.

Conclusion

Our results show that this bone ingrowth model can be employed to demonstrate the osteoconductive behavior along surfaces which display only minor differences in complexity of their microtopography.

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Acknowledgements: CIHR Fellowship (VCM), Grants from ORDCF and BIOMET ***3i,*** Palm Beach Gardens, Florida (JED)

Nanometer-scale CaP Enhances Early Implant-Bone Fixation In An Animal Model

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European Association For Osseointegration

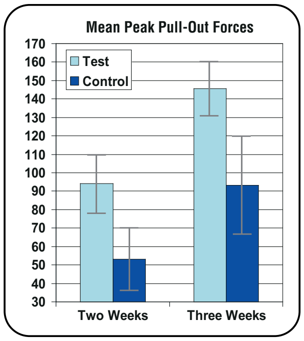
15th Annual Meeting (October 5–7, 2006, Zurich, Switzerland)

Introduction

This study used an established rabbit tibia pull-out model to demonstrate early bone fixation of implants treated with a discrete crystalline deposition (DCD) of nano-scale calcium phosphate (CaP) on a dual-acid-etched (DAE) surface.

Materials And Methods

Twenty six-month-old New Zealand white rabbits were assigned to two treatment groups. Control implants were 3.3mmx4mm Ti-6Al-4V-alloy with the DAE surface. Test implants were of the same design with the addition of DCD nano-scale CaP. One of each implant was surgically placed in the right antereomedial tibia of each rabbit 15mm apart, alternating medial and distal sites between animals. Radiographs were obtained to demonstrate uniformity of implant placement. The first treatment group was sacrificed after two weeks and the second group after three weeks. Each tibia was dissected in whole, mounted and stabilized in a precision alignment apparatus. A standard Instron machine (Model #TTMBL) was attached to apply tensile forces along the long axis of the implant. The peak pull-out force to detach the implant from bone was electronically measured and recorded.



Results And Discussion

Mean peak pull-out forces for Test implants were 94.0±33.6 N at two weeks and 145.6±19.8 N at three weeks. Mean forces for Control implants are 53.2±24.1 N at two weeks and 93.2±44.9 N at three weeks and $P<0.05$ between groups at both time points.

Conclusion

After two and three week healing periods, a significant increase in peak pull-out forces was observed for DAE implants with DCD nano-scale CaP in comparison to implants treated with DAE alone.

Discrete Calcium Phosphate Nanocrystalline Deposition Enhances Osteoconduction On Titanium-based Implant Surfaces

Vanessa C. Mendes, John E. Davies, Institute of Biomaterials and Biomedical Engineering, Faculty of Dentistry, University of Toronto, Ontario

Academy Of Osseointegration

22nd Annual Meeting (March 8-10, 2007, San Antonio, Texas)

Introduction

The surface microtopography of implants influences biological response in the peri-implant compartment by enhancing early peri-implant healing and promoting increased bone-implant contact (BIC). A recent technology has been developed, in which nano-structured calcium phosphate (CaP) crystals are deposited onto microtopographically complex titanium surfaces, adding another level of complexity to them. Our study was aimed at analyzing and comparing osteoconduction, measured as BIC, on micro and nano-textured titanium implant surfaces, using a bone ingrowth chamber model.

Materials And Methods

Custom T-shaped bone ingrowth chambers were fabricated from either commercially pure titanium (cp) or titanium alloy (Ti64). All chambers were dual-acid-etched (DAE) and half of them were modified by a discrete crystalline deposition (DCD) of CaP on the surface. Four groups were generated (cp, cpDCD, Ti64, Ti64DCD) with a total of 130 implants placed into both femora of male Wistar rats for nine days. After harvesting, samples were resin embedded and back-scattered electron images of multiple planes of the implant chambers were produced. Quantitative analysis of BIC was performed on a total of 1087 micrographs.

Results And Discussion

This bone ingrowth model was effective to demonstrate the osteoconductive behavior along surfaces with differences in complexity of their microtopography. Newton-Coles numerical integration formula was used to determine bone ingrowth as a function of anatomical location of the chamber opening and the implant surface. All groups exhibited osteoconduction, but Ti64 groups showed a higher chance to grow more bone than cp, although this was not statistically significant. However, osteoconduction on both DCD groups (26.95% cpTiDCD, 29.73% Ti64DCD) was statistically significant when compared to the results of non-DCD groups (12.01% cpTi, 16.97% Ti64). The proximal opening of the chamber consistently showed significantly higher bone ingrowth (17.49% cpTi, 30.37% cpTiDCD, 23.19% Ti64, 34.88% Ti64DCD) than the distal side (8.31% cpTi, 24.46% cpTiDCD, 12.60% Ti64, 25.55% Ti64DCD). This can be explained by the direction of the predominant blood supply to the distal femur.

Conclusion

The DCD enhanced osteoconduction during early stages of peri-implant healing and that the anatomical location plays an important role in bone growth in this model.

Discrete Calcium Phosphate Nanocrystals Render Titanium Surfaces Bone Bonding

Vanessa C. Mendes, John E. Davies, Institute of Biomaterials and Biomedical Engineering, Faculty of Dentistry, University of Toronto, Ontario

Academy Of Osseointegration

22nd Annual Meeting (March 8-10, 2007, San Antonio, Texas)

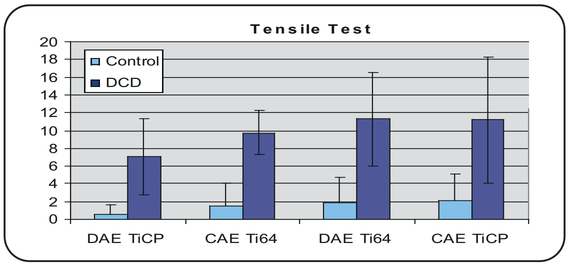
Introduction

Recently, an already clinically successful microtextured metallic surface has been modified by the discrete crystalline deposition (DCD) of nano-crystals of calcium phosphate (CaP). These deposited crystals have little effect on the micron-scale texture of the metallic surface, but do superimpose upon it a nano-scale topographical complexity. The purpose of the present study was to design an experiment to answer the question: Can such DCD render a metallic implant surface bone-bonding?

Materials And Methods

Custom designed rectangular implants, 1.3x2.5x4mm, were fabricated from either commercially pure (cp) or titanium alloy (Ti6Al4V or Ti64). Implants were either dual-acid-etched (DAE) or treated by a citric acid based process (CAE), and half of the implants were modified by the DCD. Eight groups were generated and implants were placed bilaterally into the femora of 48 male Wistar rats for nine days. After harvesting, the femora were trimmed to the width of the implant, resulting in two cortical arches of bone attached to each implant. The implant was attached an Instron™ Testing Machine and the arches of bone were distracted at 30mm/min. The force to rupture the sample was recorded. Field emission scanning electron microscopy (FE-SEM) was used to analyze the bone/implant interface following detachment.

The post-operative period was uneventful except for one rat, which had problems load-bearing and was excluded from the study. Two samples were compromised while being positioned in the Instron machine. Sixty one arches (16 cpDAE, 2 cpDAE-DCD, 12 Ti64DAE, 2 Ti64DAE-DCD, 13 cpCAE, 14 Ti64CAE and 2 cpCAE-DCD) were insufficiently attached to the surface of their implant to withstand handling, and thus were included as zero. The resulting 129 arches were mechanically tested. DCD surfaces had statistically significantly greater average values of detachment force (cpDAE-DCD 7.08N, Ti96DAE-DCD 11.30N, cpCAE-DCD 11.19, Ti64CAE-DCD 9.74) than non-DCD (cpDAE 0.60N, Ti64DAE 1.90N, cpCAE 1.49, Ti64CAE 9.74). The bone-bonding phenomenon was visually evident when the cortical arches were fractured and the bone/implant interface remained intact. Globular accretions similar to those of cement lines were observed microscopically, by FE-SEM, interdigitating with the surface of the implant. We conclude that titanium implant surfaces can be improved and rendered bone-bonding by nano-structured CaP surface modification.



*Randomized/Controlled Histological And Histomorphometric Evaluation Of NanoTite™ And Control Site Evaluation Implants (SEI) In The Human Posterior Maxilla**

Giovanna Orsini, Maurizio Piattelli, Antonio Scarano, Giovanna Petrone, James Kenealy, Adriano Piattelli, Sergio Caputi - Accepted for Oral Presentation University Foundation and Department of Stomatology and Oral Science, University of Chieti-Pescara, Italy

Academy Of Osseointegration

22nd Annual Meeting (March 8-10, 2007, San Antonio, Texas)

Introduction

Placement of dental implants in the posterior maxilla has been associated with higher rates of failure due in part to the poor bone quality in this region. Implant osseointegration has been improved by introducing different surface treatments. The purpose of the present study is the histological and histomorphometric evaluation of bone formed around a new implant surface that is created by a deposition of nanometer-sized calcium phosphate particles added to the OSSEOTITE® Dual-acid-etched surface.

Materials And Methods

One Test (NanoTite) and one Control (OSSEOTITE) custom-made 2mm x 10mm site evaluation implants (SEI) were placed in the posterior maxilla of 15 patients. All SEIs were retrieved after two months and evaluated under light microscopy and confocal laser scanning microscopy (CLSM) for histomorphometric analysis of the bone-implant contact (BIC).

Results And Discussion

The mean BIC values for Test and Control SEIs are 32.2±18.5% and 19±14.2% respectfully. A statistical analysis of this 70% difference between BIC values for Test and Control implants is significant at the $p<0.05$ level. Histological observations of Control SEI show formation of new bone around the implant surface that was not always in direct contact with the entire perimeter of the threads. Test SEI show peri-implant bone tightly contacting the implant surface and better adapted to the threads. Three-dimensional reconstruction of sections obtained using CLSM display the stereographic structure of the bone-implant interface through the entire thickness of the histological slide, showing the intimacy of the contact between bone and test surfaces.

Conclusion

In this first human evaluation of the NanoTite Surface, histological and histomorphometric results show enhancement of new bone formation in early healing time periods. Clinical implications of these results include shortening of implant healing period and earlier loading protocols.

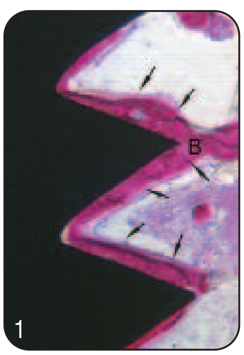


Figure 1: Histologic view of test SEI. The bone (B) is adapted well to the entire perimeter of the implant threads (arrows). (Acid fuchsin and toluidine blue; original magnification ·10.)

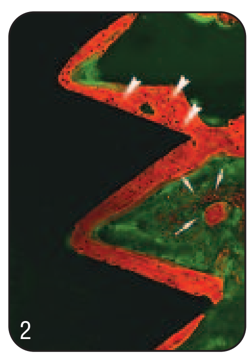


Figure 2: The CLSM image allows improved identification of osteocytes (arrowheads) in the peri-implant bone and helps in the detection of some newly formed bone

CLSM = confocal laser scanning electron micrograph

Credit: Department of Stomatology and Oral Science, University of "G. d'Annunzio" of Chieti-Pescara

*Full study accepted for publication: ***Randomized, Controlled Histologic and Histomorphometric Evaluation of Implants With Nanometer-Scale Calcium Phosphate Added to the Dual Acid-Etched Surface in the Human Posterior Maxilla.*** *J Periodontol* 2007;78:209-218

Overview: Studies In Progress

The following clinical protocols are either ongoing or about to be launched. A brief description of the project and its goals and objectives are described:

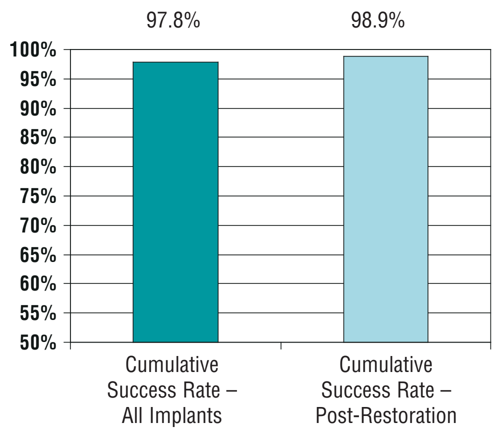
NanoTite™ Clinical Research Activity - translating preclinical results to clinical benefits

Preclinical and bench-top studies offer opportunities for determining differences between various prototype designs. The preclinical studies from UCLA and The University of Toronto go a long way to confirming that the addition of the Discrete Crystalline Deposition™ Treatment imparts a substantive improvement as compared to standard OSSEOTITE®.

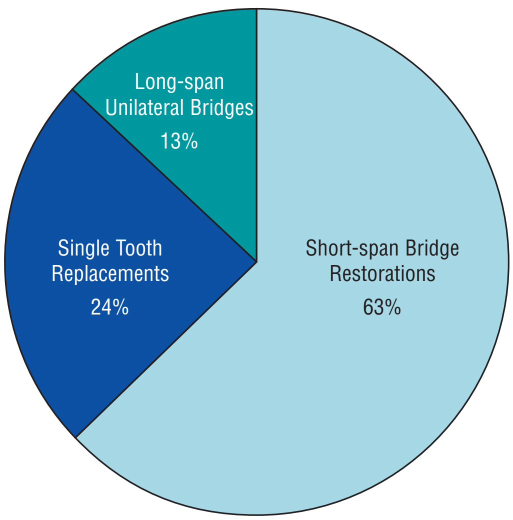
But will this matter in clinical cases? What exactly can we look to offer in terms of benefits to the clinician and patient? These and other studies to follow will provide evidenced-based data to allow clinicians to understand how they can derive additional benefit from BIOMET ***3i*** NanoTite Implants. What follows are the various ongoing research activities being conducted on the NanoTite Implant.

Immediate Loading – Study 2601 is a prospective observational study of NanoTite PREVAIL® Implants used for immediate loading of single tooth restorations and unilateral bridge cases. The goal of this project is to recruit, treat and monitor the progress of a large group of patients having a provisional restoration attached within 48 hours. Fifteen study centers located in North America, Europe and Australia participate in this five year clinical trial. The enrollment phase is now complete and the interim results are providing the reassurance that was hoped for in bringing the benefits of immediate loading with the same overall implant success rates observed for early- and delayed-loading cases. A manuscript of the initial results is being prepared for publication.

As of Dec 31, 2006, 145 patients having 189 cases supported by 282 implants are being monitored with over 74 patients having exceeded 12 weeks of on-going evaluation. Case distribution is: short-span bridge restorations (53%), single tooth replacements (24%) and long-span unilateral bridges of five units or greater (13%). Six implants have been reported as failures resulting in a 97.8% overall success rate. As three of the six were the result of an immediate post-surgical infection in one patient, the cumulative success rate post-restoration is 98.9%.



Cumulative Success Rates



NanoTite PREVAIL Implant Cases Under Evaluation

Overview: Studies In Progress

Human Clinical Studies

Fully Edentulous Maxilla – Study 2607 is a prospective, randomized-controlled study of fully edentulous maxilla patients where cases will be randomly assigned to receive either the NanoTite™ or OSSEOTITE® Surface Implant. The study will assess the integration success and duration of failure-free function of all implants to determine if the NanoTite Surface enhancement can improve performance in fully edentulous maxillary cases.

Placement In Augmented Bone – Study 2604 is a prospective, randomized-controlled comparison of NanoTite PREVAIL® Implants used in sinus lift augmentation sites. The goal of this multicenter study is to determine if the NanoTite Surfaced Implants placed simultaneously with the sinus augmentation graft material have the same success outcomes as do NanoTite Implants placed into healed sinus augmentation grafts. When this is established, there will be the opportunity to avoid four months of delay in functionalizing such sinus augmentation cases.

Immediate Replacement In Extraction Sites – Study 2605 is a prospective, randomized-controlled study of patients with multiple tooth extractions where at least two sites will be randomly assigned to receive either the NanoTite or OSSEOTITE Surface PREVAIL Implant. The study will assess the integration success and duration of failure-free function of all implants to determine if the NanoTite Surface enhancement can improve performance in these more challenging cases.

Sinus Augmentation Avoidance Trials – Studies 2611 and 2612 will utilize a 7mm length NanoTite Surface Implant (actual length – other "short implants are actually 7mm or longer) to be used in thin maxillary cases where a sinus augmentation (and standard length implants) would be utilized. In addition to assessing integration and duration of failure-free performance of these short implants, a specific effort will be made to quantify the amount of resources (clinician and patient time and discomfort, surgical costs, materials costs) that can be preserved by obviating the need for an augmentation surgery.

Implant Stability – Study 2610 is a randomized, double-blind evaluation of the impact of a surface modification on the Implant Stability Quotient during the initial implant healing period. This prospective, double blind, randomized-controlled clinical study will evaluate changes in the implant stability quotient (ISQ) that take place within the first eight weeks following implant placement in the posterior mandible and maxilla to determine if a difference in the ISQ measurements are detected between OSSEOTITE and NanoTite Implants.

Clinical Comparisons Of NanoTite Vs. OSSEOTITE Histomorphometric Outcomes –
University G. d'Annunzio, Chieti-Pescara University, Italy
Miniplants of 2mm diameter and 10mm length are placed in the posterior maxilla at sites that will later receive clinical implants are retrieved after about two months healing and subjected to histological analysis of bone-to-implant contact. NanoTite and OSSEOTITE Surfaced Miniplants are placed in the same patient to provide patient-controlled outcomes. Results of this accepted for presentation at the upcoming Academy of Osseointegration 2007 Symposia in San Antonio.

Biomaterials Clinical Research Association, Pescara, Italy
NanoTite and OSSEOTITE Surfaced Miniplants placed in the posterior maxilla and retrieved after two months healing are processed for histological analysis of bone-to-implant contact.

Animal Pre-Clinical Studies

Soft And Hard Tissue Analysis Of NanoTite And OSSEOTITE Implant Surfaces –
The Sahlgrenska Academy at Göteborg University
Eight implant sites in each of six canine animals are randomly assigned to receive either NanoTite or OSSEOTITE Transgingival Implants where the surfaces extend from the apex to the coronal seating platform. After two and four weeks of healing, the interfacial tissues are examined by ground section and by a fractionation method that allows observation of microcellular structures.

Soft And Hard Tissue Analysis Of NanoTite And OSSEOTITE Implant Surfaces –
A collaborative research effort of the Universities of Madrid, Sienna and Göteborg
Four implant sites in each of six canine animals are randomly assigned to receive either NanoTite or OSSEOTITE Implants that are placed in a single-stage manner with corresponding NanoTite and OSSEOTITE Healing abutments. After two and four weeks of healing, the interfacial tissues are examined by ground section and by a fractionation method that allows observation of microcellular structures.

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