Research Dossier Roadmap

The NanoTite™ Implant
At-A-Glance Abstract Listing

Surface Characterization Studies

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

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A means of modifying titanium surfaces with Calcium Phosphate (CaP) has been developed that comprises the deposition of discrete crystals (DCD™) of CaP (20-100 nm) onto the metal surface of a dental implant. This study was designed to quantify the amount and dissolution kinetics of these discrete CaP crystals from dental implant surfaces and compare their behavior with commercially-available plasma sprayed CaP coated implants of a similar size. The results showed that DCD-treated Implants had 3 orders of magnitude less CaP than plasma sprayed implants. Furthermore, at normal body pH of 7.4, the dissolution of CaP from DCD Implants is almost zero, while dissolution continues to occur from plasma sprayed implants. DCD Treatment provides the surface with the advantages of CaP while utilizing more than 3000 times less coverage than traditional plasma spraying. The treatment also retains a homogenous and stable phase of CaP compared to the more soluble and hence undesirable multi-phase CaP coverage achieved through plasma spraying.

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

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

This study estimates the increase in surface area (SA) due to the Discrete Crystalline Deposition of nano-scale Calcium Phosphate (CaP) onto a dual acid-etched (DAE) implant surface. The calculated estimates for an SA increase due to the deposition of CaP nanocrystals were 84%, 152% and 264% for 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 nanometer-scale CaP onto the DAE surface ranges from 176%-446%. The results show that deposition of nano-scale CaP crystals over a micron-scale DAE surface significantly increases the overall SA and topographical complexity of the implant surface.

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

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The objective of this study was to characterize the surface roughness of polished titanium disks with nanometer-scale Calcium Phosphate (CaP) crystals deposited by Discrete Crystalline Deposition (DCD). Atomic Force Microscopy (AFM), widely employed to quantify surface measurement parameters of nanometer topographical characteristics, was used to obtain surface maps. The surface roughness characterization 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

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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. The average crystal-surface adhesion shear strength analysis was 1.75GPa for CPTi and 1.52GPa for Ti Alloy. The maximum torque for implant placement was 17N-Cm, which resulted in an average shear stress of 3.61x10-4GPa at the implant-bone interface. The maximum shear stress, occurring at the fore threads in the apical zone, was 5.14x10-1GPa. The average CaP 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 CPTi or Ti Alloy DAE surfaces will not dislodge during implant placement.

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

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The strength of the bond between the implant surface and nanometer-scale Calcium Phosphate (CaP) crystals can be used as an indicator of the likelihood of the crystals becoming dislodged during implant placement. The objective of this experiment was to determine the shear strength of the crystals deposited on an OSSEOTITE® Implant Surface using contact-mode AFM analysis. This test employed 20mm disks, three each of commercially pure titanium (CPTi) and titanium alloy (Ti-Alloy) in which thirty (30) crystals were sheared and the shear forces were measured. The crystals on the CPTi substrate had an average strength 15% higher than the crystals on the Ti Alloy surface.

See ART990 for a complete summary of these studies and other studies in progress.

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

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The objective of this test was to qualitatively assess if nanometer-scale CaP crystals discretely that were bonded to OSSEOTITE® Implants would dislodge during placement and removal in a simulated bone material. Ti-Alloy and CpTi OSSEOTITE Implants with nanometer-scale CaP crystals were screwed into and removed from a simulated bone medium. The implants were then imaged with a field emission scanning electron microscope (FESEM) and compared to controls to determine if the crystals became dislodged. Based on the imaging results, these CaP nanocrystals did not become dislodged during implant placement and removal.

Modeling Interfacial Shear Strength At A CAP-Modified Titanium And Bone

Chunpo Pan, Jason Chau, Vanessa C. Mendes, Craig A. Simmons and John E. Davies
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This study is a follow up to previous work which demonstrated that discrete calcium phosphate nanocrystals rendered titanium implants Bone Bonding™*. It sets out to answer the question; can the Bone Bonding Phenomenon be achieved exclusively by a micro-mechanical interlocking mechanism? The model was designed to predict whether failure of the bone or failure of the TiO_2/CAP interface would occur for a given tensile load. The results demonstrated that the CAP-modified implants can withstand high stress loads (44 KPa pressure) because of mechanical interlocking and shows that the Bone Bonding Phenomenon can be achieved exclusively by micro-mechanical interdigitation. The results also indicated that the bone fails before the TiO_2/CAP interface, which is in accordance with in-vivo experimental results.

Chemical And X-ray Diffraction Analysis Of Calcium Phosphate Used For Discrete Crystalline Deposition™

Renée M. Stach, Prabhu Gubbi and Zach Suttin, BIOMET ***3i,*** Palm Beach Gardens, Florida, USA

The two-part objective of this study was (1) to confirm that the CaP particles in the colloidal solution used for the DCD™ Process have a predetermined crystallinity and chemistry that are not altered during the application process to the titanium surface and (2) to qualitatively assess the size and shape of the CaP particles deposited on the implant surface using Field Emission Scanning Electron Microscopy (FESEM). The X-ray Diffraction (XRD) analysis of both the source material sample used for preparing the colloidal solution and the dried CaP sample that had been used in the DCD Process show 100% crystallinity within the detection limits of the instrumentation. No amorphous content was detected. The FESEMs of the implant surface show discrete depositions of CaP crystals. The size, shape and structure of the CaP crystals visually appear to be in the size range from 20nm to 100nm, which is in agreement with the Certificate of Analysis from the manufacturer of raw CaP powder. By incorporating highly crystalline CaP crystals into a nano-scale textured surface, the biological benefits of hydroxyapatite and the osseogenic potential of surfaces with nanotopographical features can be realized in-vivo.

Hydrophobic/Hydrophilic Characteristic Of Titanium Surfaces: Machined, Dual Acid Etched (OSSEOTITE) And Dual Acid Etched With Nanometer-Scale CaP (NanoTite™)

Prabhu Gubbi, Ross Towse and Bruce Berckmans, BIOMET ***3i,*** Palm Beach Gardens, Florida, USA

Contact angle, reported in degrees, is a measure of the wetting of a solid surface by a liquid. The objective of this study was to measure the static contact angle made by liquid media on various titanium surfaces and determine whether a given surface was hydrophobic or hydrophilic. The static contact angle is mainly affected by two factors, surface topography or morphology and surface chemistry. The evaluation of the various surfaces indicates a clear correlation between the complexity of the surface topography and its hydrophilic or hydrophobic nature; the increase in surface complexity had a direct effect on rendering the surface increasingly hydrophobic.

Qualitative And Quantitative Analysis Of NanoTite Surfaced Implants

Prabhu Gubbi and Ross Towse, BIOMET ***3i,*** Palm Beach Gardens, Florida, USA

The objective of this study was to characterize the surface of experimental implants treated with a new proprietary surface treatment called Discrete Crystalline Deposition (DCD) of nanometer-scale calcium phosphate. The particle size of the nano-CaP crystals used as a raw material in the DCD Process ranged from 20nm to 70nm. By controlling the various process variables, it was possible to achieve different categories of surface coverage, classified as light (25-30%), medium (55-60%) and heavy (80-85%). From the analysis of high resolution images obtained by FESEM, it was determined that the particle size (20nm to 70nm) did not change significantly from the raw material and that the particles retained their crystalline nature after processing.

Note: commercial product (i.e. the NanoTite Implant) has medium CaP coverage.

*Bone Bonding is defined as the interlocking of the newly formed cement line matrix of bone with the implant surface.

Preclinical Animal Studies

Implants Treated With Discrete Crystalline Deposition™ Of Nanometer-Scale Calcium Phosphate Crystals Enhance Early Implant-Bone Fixation In A Rat Femur Push-In Model

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The topography and biochemical properties of titanium implant surfaces influence the rate and extent of adherent *de novo* bone formation. This study uses a rat femur push-in model to demonstrate early bone fixation of implants treated with Discrete Crystalline Deposition (DCD™) of nanometer-scale calcium phosphate crystals added to a dual acid-etched (DAE) surface. Twenty-four male rats received one Test implant and one Control implant and were then sacrificed after 4, 7 and 14 days of healing. Measurement of mean peak push-in forces at 4, 7, and 14 days for Test implants exhibited a substantial increase of mechanical resistance from day 4 to day 7 and from day 7 to day 14. This study demonstrated a significant increase in bone fixation for Test implants at 14 days, and suggests that while the DCD Surface Treatment did not alter the predisposing surface microtopography of the DAE implant substrate, the nanometer-scale calcium phosphate crystals appear to affect early implant fixation processes by a potentially unique mechanism.

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

James N. Kenealy, Bruce Berckmans and Renée M. Stach, BIOMET ***3i,*** Palm Beach Gardens, Florida, USA

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. Twenty six rabbits were assigned to two treatment groups to be sacrificed after either two or three weeks. One test and one control implant was placed into the right tibia. After sacrifice, each tibia was dissected in whole, mounted and stabilized in a precision alignment apparatus. A standard Instron™ testing machine 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 show that 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, Canada

This study was aimed at analyzing and comparing osteoconduction, measured as Bone-to-Implant Contact (BIC), on micro and nano-textured titanium implant surfaces, using a bone ingrowth chamber model. A total of 130 implants were placed into the femora of rats for nine days. After harvesting the samples, quantitative analysis of BIC was performed on 1087 micrographs. Results showed that osteoconduction on the Discrete Crystalline Deposition (DCD) Implant Groups was statistically significant when compared to the results of non-DCD Groups, consistently showing higher bone ingrowth.

Discrete Calcium Phosphate Nanocrystals Render Titanium Surfaces Bone Bonding™*

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

The purpose of this study was to determine if Discrete Crystalline Deposition (DCD) of nanocrystals of calcium phosphate (CaP) can render a metallic implant surface Bone Bonding. Dual acid-etched (DAE) implants, with and without DCD, were placed into the femora of 48 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 cortical bone of the implants was threaded with nylon lines. These lines were then attached to an Instron testing machine, displaced at 30mm/min and the force to rupture the sample was recorded. Field emission scanning electron microscopy (FESEM) was used to analyze the bone/implant interface following detachment. A total of 63 samples were tested. High detachment forces were observed with the DCD treated samples when the bone arches fractured leaving the bone/implant interface intact. The results demonstrate that DAE implant surfaces can be improved and rendered Bone Bonding by nano-structured CaP surface modification.

*Bone Bonding is defined as the interlocking of the newly formed cement line matrix of bone with the implant surface.

See ART990 for a complete summary of these studies and other studies in progress.

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

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

This study presents results that show that etched titanium alloy is more osteoconductive than commercially pure (cp) titanium. Further, when modified by Discrete Crystalline Deposition™ (DCD™) of nano-scale deposits of calcium phosphate, osteoconduction on both metals is significantly increased. A total of four groups of 25 Tplants: cp, cp with DCD, alloy and alloy with DCD were generated. Osteoconduction was identified by bone growth along the walls of the implant. Osteoconduction on both DAE with DCD Groups (cp and alloy) was significantly enhanced in all levels of analysis. This was statistically significant when compared to the results of DAE without DCD Groups in all levels of analysis. Also, statistically significant differences were verified with respect to increased values of osteoconduction for titanium alloy compared to cp.

Discrete Calcium Phosphate Nanocrystals Render Titanium Surfaces Bone Bonding™*

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

The purpose of this study was to determine if Discrete Crystalline Deposition (DCD) of nanocrystals of calcium phosphate (CaP) can render a metallic implant surface Bone Bonding. Dual acid-etched implants, with and without DCD, were placed into the femora of 48 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. A total of 129 arches were mechanically tested with 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 (FESEM) was used to analyze the bone/implant interface following detachment. The results of this study demonstrated that a 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 FESEM, 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.

Discrete Deposition Of Hydroxyapatite Nanoparticles On A Titanium Implant With Predisposing Substrate Microtopography Accelerated Osseointegration

Ichiro Nishimura, Frank Butz, Takahiro Ogawa, Audrey Lin and Chiachien Jake Wang, UCLA School of Dentistry, The Weintraub Center for Reconstructive Biotechnology and Division of Advanced Prosthodontics, Biomaterials and Hospital Dentistry, Los Angeles, CA, USA, Yuhong Huang, Chemat Technology, Incorporated, Northridge, CA, USA

A new method of depositing discrete hydroxyapatite (HA) nanoparticles on a titanium (Ti) implant exhibited an unexpectedly robust biological effect. As a result, the discrete deposition of HA nanoparticles generated novel 20–40nm nanotopography on the Ti substrate. A force push-in test demonstrated that the deposition of HA nanoparticles on the DAE surface increased the mechanical withstanding load by 129% and 782% as compared to the control DAE and turned implants. These data suggest that the discrete deposition of HA nanoparticles accelerates the early osseointegration process, likely through increased shear bonding strengths.

Discrete Deposition Of Calcium Phosphate Nanocrystals Promotes Bone Bonding On Titanium Surfaces

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It has been found that it is possible to modify an already clinically successful microtextured metallic surface by the Discrete Crystalline Deposition (DCD) of nano-crystals of calcium phosphate (CAP). These deposited crystals superimpose upon it a nano-scale topographical complexity. In this study custom implants were fabricated from either commercially pure titanium or titanium alloy. All implants were dual acid etched. A total of 8 groups (2 non-DCD and 6 DCD) were generated and placed in the femora of rats for 9 days. A total of 169 cortical bone arches were tested. Comparative tensile forces showed that the non-DCD Groups were the same ($p=0.3925$). However, the average of tensile forces for the non-DCD Groups was statistically significantly lower than for DCD Groups ($p<0.05$). The DCD Surface Treatment renders the implant surface Bone Bonding, which was demonstrated by the fracture of the bone above the bone-implant interface.

*Bone Bonding is defined as the interlocking of the newly formed cement line matrix of bone with the implant surface.

See ART990 for a complete summary of these studies and other studies in progress.

Human Histological Studies

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

This study is a histological and histomorphometric evaluation of bone formed on a new implant surface that is created by a deposition of nanometer-sized calcium phosphate particles added to a dual acid-etched (OSSEOTITE®) Surface. 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 and retrieved after two months. The mean BIC values for Test and Control SEIs are 32.2±18.5% and 19±14.2% respectfully. After 2 months of healing, comparison of the BIC values showed a statistically significant greater mean BIC for test SEIs than for controls (70% difference). Clinical implications of these results include shortening of the implant healing period and earlier loading protocols.

Full Study results were published in the Journal of Periodontology, 2007; 78:209-218 (ART994).

Influence Of A Nanometer-Scale Surface Enhancement On De Novo Bone Formation On Titanium Implants: A Histomorphometric Study In Human Maxillae

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In this prospective randomized controlled clinical study, nine pairs of site evaluation implants were placed in posterior areas of the maxillae and retrieved with trephine drills after 4 or 8 weeks of unloaded healing. Implant surfaces were dual acid etched (controls) or dual acid etched and further conditioned with nanometer-scale crystals of calcium phosphate (test implants), and the surfaces were compared. Results show that the mean bone-to-implant contact value for the test surface was significantly increased as compared to control implants at both time intervals ($P < .01$).

Full study results were published in IJPRD, 2007; 27:3:75-91 (ART1002).

Human Clinical Studies: In Progress

Immediate Loading - This is a prospective observational study of NanoTite PREVAIL® Implants used for occlusal and non-occlusal loading of single tooth restorations and unilateral bridge cases. The goal was to recruit, treat and monitor the progress of a large group of patients having a provisional restoration attached within 48 hours. Fifteen study centers in North America, Europe and Australia are participating in this five year clinical trial. As of August 2007, 190 patients having 220 cases supported by 343 implants are being monitored with all patients having exceeded 12 months of on-going evaluations. To date, the cumulative success rate post-restoration is 96.8%.

Fully Edentulous Maxilla - This is a prospective, randomized-controlled study of fully edentulous maxilla patients where cases will be randomly assigned to receive either the NanoTite or OSSEOTITE Surfaced 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 - This 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 delays in functionalizing such sinus augmentation cases.

Immediate Replacement In Extraction Sites - This 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 challenging cases.

See ART990 for a complete summary of these studies and other studies in progress.

Human Clinical Studies: In Progress

Sinus Augmentation Avoidance Trials - These studies 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 eliminating the need for an augmentation surgery.

Implant Stability - This 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.

Animal Pre-Clinical Studies: In Progress

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.

See ART990 for a complete summary of these studies and other studies in progress.