www.jmscr.igmpublication.org Impact Factcor-1.1147
ISSN (e)-2347-176x

IGM Publication Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

A New Horizon for Better Dental Implants – A Nanotechnological Approach

Authors

Dr Laxmi Chhuchar[1], Dr Hiroj Bagde[2], Dr Nitin Lokhande[3]

Dr Abhishek Bezalwar[4]

[1,2,3,4]ACPM Dental College, Sakri road, Dhule,Maharashtra,India

Email: drlaxmichhuchhar@yahoo.com, hiroj.bagde@gmail.com, drnlokhande@gmail.com, abhishekbezalwar@gmail.com

ABSTRACT

Current trend in dental implants include use of endosseous dental implant surfaces embellished with nanoscale topographies. The goal of this review is to consider the role of nanoscale topographic modification of titanium substrates for the purpose of improving osseointegration. There is a strong belief that nanoscale materials will produce a new generation of implant materials with high efficiency, low cost, and high volume. The nanoscale in materials processing is truly a new frontier. Metallic dental implants have been successfully used for decades but they have serious shortcomings related to their osseointegration and the fact that their mechanical properties do not match those of bone. Nanoscale modification of titanium endosseous implant surfaces can alter cellular and tissue responses that may benefit osseointegration and dental implant therapy. This paper reviews recent advances in the fabrication of novel coatings and nanopatterning of dental implants. Important distinctions between nanoscale and micron-scale modification of the implant surface are presently considered. It also provides a general summary of the state of the art in dental implant science and describes possible advantages of nanotechnology for further improvements.

Keywords-Implants, Nanoscale, osseointegration, Nanotechnology, implant surface.

Introduction

Replacement of tooth and bone with metal implants and plates is one of the most frequently used and successful surgical procedures. Current dental implant success has evolved from modest results of the middle of the past century. Beginning in the late 1960s the focused efforts of PI Branemark led to the detailed microscopic characterization of interfacial bone formation at machined titanium endosseous implants [1,2]. These concepts of osseointegration focused the profession on a proscribed surgical technique and the biocompatible nature of the machined titanium surface. Bone formation at the endosseous implant surface was considered a positive outcome that was contrasted to fibrous encapsulation, a negative and undesired result [3]. After decades of subsequent research in industry and academia, implants have evolved, with a high

percentage of survival rate and longevity. The research resulted in better design, better materials, and more extensive clinical experience compared with the early years of implant development. One can argue, however, that the progress has been slow and incremental. We are still using almost the same alloys described in the works of Branemark and Charnley, many of which were originally developed by the aerospace industry.

Dental implants have a long and successful history. The percentage of failure is very low, approximately 5%, mostly likely due to infection, rejection, accelerated bone loss, and poor osseointegration with loosening of the implant [4]. The most frequent cause for failure is insufficient bone formation around the biomaterial immediately after implantation [5]. Therefore, this is an area where improvements are needed. This is becoming even more important as clinicians are pushing for faster healing times. Challenging osseointegration with new protocols such as immediate placement and immediate loading may require further control of bone formation and osseointegration [6]. Consequently most modifications in the implant design are geared toward reducing the time needed to wait before loading. It is here that the implant surface and tissue interface are critical [7]. Current surface chemistries and morphologies are controlled, at best, at the micron level, but tissue response is mainly dictated by processes controlled at the nanoscale. Understanding and controlling interfacial reactions at the nano level is the key to developing new implant surfaces that will eliminate rejection and promote adhesion and integration to the surrounding tissue.

Nanotechnology and surface science:

Nanotechnology has been defined as ‘‘the creation of functional materials, devices and systems through control of matter on the nanometer length scale (1–100 nm), and exploitation of novel phenomena and properties (physical, chemical, and biological) at that length scale’’ (National Aeronautics and Space Administration). Nanotechnology involves materials that have a nano-sized topography or are composed of nano-sized materials; in the size range between 1 and 100 nm (10-9 m) Nanotechnology often involves one-dimensional concepts (nanodots and nanowires) or the self-assembly of more complex structures (nanotubes). Materials are also classified according to their form and structure as nanostructures, nanocrystals, nanocoatings, nanoparticles, and nanofibers [5].

Application of nanotechnology to the dental implant surface involves a two dimensional association of surface features (across and away from the mean surface plane). These nanofeatures can be arranged in an organized manner (isotropic) or unorganized manner (anisotropic), often depending on the method of manufacture. Anisotropic topography is mostly applied to a dental implant surface. When these concepts are applied to the endosseous implant surface, implied is the embellishment of the surface with nanometer-scale features that lead to novel Physicochemical behavior (e.g. bone bonding) or biochemical events (e.g. altered protein adsorption, cell adhesion with changes in cell behavior).

Nanoscale modification of the titanium endosseous implant surface may affect both the topography as well as the chemistry of the surface. Albrektsson and Wennerberg [8] divided implant surface quality into three categories: (1) mechanical properties, (2) topographic properties, and (3) physicochemical properties. They indicated that these characteristics are related and by changing any of these groups the others will also be affected.

Surface modifications of dental implants:

1. Ceramic coatings:

Various coatings have been developed to improve an implant’s ability to bond to living tissues, particularly bone. This thin ceramic layer will bond both to the implant and to the surrounding tissue while promoting bone apposition. These materials are bioactive compounds able to promote cell attachment, differentiation, and bone formation. The most prevalent bioactive materials are calcium phosphates (CP), such as hydroxyapatite (HA) or tricalcium phosphate (TCP), and bioactive glasses. When implanted, these bioactive ceramics form a carbonated apatite (HCA) layer on their surfaces through dissolution and precipitation. This phase is equivalent in composition and structure to the mineral phase of osseous tissue. At the same time, collagen fibrils can be incorporated into the apatite agglomerates. The sequence of events is poorly understood but appears to be: adsorption of biological moieties and action of macrophages, attachment of stem cells and differentiation, formation of matrix, and, finally, complete mineralization [9–13].

Ideally, the coatings should be tailored to exhibit prescribed biological attributes for each specific application. They should have strong adhesion to the implant and good fixation to bone. Their

microstructure and dissolution rates must be programmed to match the in vivo healing process, and they could serve as templates for the in situ delivery of drugs and growth factors at the required times. Essential requirements of the new family of coatings include: (1) good adherence to the implant, (2) fixation to the bone, (3) fine gradient and thickness control with programmed dissolution rate in body fluids, and (4) therapeutic capabilities. These are discussed below.

Coating/implant adherence: Currently available coating techniques provide inadequate adherence of CP coatings to Ti alloys. Quoted bond strengths, 15–30 MPa, are very low [14-17].

Interfacial strength and toughness are needed to optimize the mechanical stability of the coatings. A need to develop standard procedures to test adhesion, and a clear understanding of the mechanisms of interfacial failure in the body environment is required.

Fixation to bone—

Two primary modes of attachment are: (1) mechanical, in which the implant has a rough, porous surface into which bone grows (often supplemented by use of a bone cement); and (2) chemical, in which bone "bonds" to the implant material. Here it is difficult to decouple the effect of coating chemistry and topography. Dissolution of calcium and phosphorus from the coating may promote mineralization and bone formation but it is not clear how much coating solubility contributes to the best fixation, and excessive resorption can limit implant lifetimes [18,19]

Programmed dissolution rates—A critical goal in the design of novel coatings is the programming of their dissolution (bioresorption) rates. [20]. Graded coatings designed with a soluble surface to facilitate bonding to bone and an insoluble layer in contact with the metal to provide adhesion, corrosion resistance, and long-term mechanical stability could offer a significant improvement over current materials. Both the composition and thickness of the graded coating layers can be controlled to manipulate the resorption rates. Their resorption can be programmed to match healing rates and to expose different microarchitectures, chemical patterns, and porosities at different times to optimize the biomaterial coating surface for different periods of the healing-in phase.

Drug delivery— Inflammatory responses to implants are a significant problem. Medications that are given to a patient following surgery to suppress inflammation seem to be insufficient or entirely ineffective in many cases. [21-23]. A different approach is to provide a local dose of anti-inflammation agents gradually released from a coating on the surface of the implanted device [24,25]. The main advantage of this approach over traditional means of administering the drug is that the drug can be directly released at the implant site without having to go through the bloodstream. This lowers the amount of drug needed, reducing the overall toxicity and side effects. In addition, growth factors that are known to encourage tissue-implant integration, such as TGF-β [26,27], may be delivered locally using this platform. These chemicals could be incorporated into the porosity of micro- and nanoporous coatings or could be dispersed in biodegradable polymers, and combined with the bioactive glass/CP coatings.

Plasma Spraying Of HA: Plasma spraying of HA being the most popular method [28-33], offers only rudimentary control of the coating thickness and composition. The thickness of plasma-sprayed coatings typically exceeds 50 μm. The high process temperatures cause partial thermal decomposition of HA, leading to the formation of other CPs, including 22–62% of highly soluble amorphous calcium phosphate [34-38], α- TCP, β-TCP, tetracalcium phosphate, and calcium oxide [39-41]. The result is coatings with unacceptable heterogeneous properties. Severe problems include: (1) unreliable adhesion—they can detach, yielding floating fragments [42]; (2) continued dissolution of the coating, leading to catastrophic failure of the implant at the coating-substrate interface [43]—attempts to increase crystallinity and reduce solubility by post-coating thermal annealing markedly degrades the coating adherence [44-48]; (3) variability during processing in terms of resulting phases, stresses, and cracking [49-52]; (4) partial crystallization of the deposited coating, leading to the presence of more soluble CP compounds [53-55]; (5) significant degradation in the fatigue resistance and endurance strength of the implant alloy [56]; (6) very irregular morphology of the coatings; (7) poor control of the coating thickness, with greater risk of fracture, the thicker the coating; and (8) poor control of physicochemical properties, and hence the biological stability of the coating [57,58].

Sol-gel colloidal Particle Adsorption: Several other techniques have been used to apply CP coatings on metallic alloys, from sol-gel to RF magnetron sputtering and others [50,59,60]. These techniques may offer a more accurate compositional control

and the possibility of fabricating much thinner layers (of the order of 1 micron or less). This could be advantageous for coating stability, as the driving force for cracking and delamination decreases with the decreasing thickness. The nature of the coating and the process might be tuned in order to modify the interfacial strength

Anodic Oxidation: Another technique worth further exploration is anodic oxidation, which has been used as a means to engineer the surface of Ti-based implants [64,65]. This technique can be used to create an adherent oxide coating on the implant surface. By selecting different electrolytes and manipulating the conditions, it is possible to create oxide layers with a wide range of stoichiometries as well as micro- and nanoporosities. It is also possible to incorporate Ca and P ions into the layers. This is a relatively simple and economical technique that can be easily adapted to fabrication, and anodized implants are commercially available.

2. Surface functionalization:

An alternative or complementary strategy to the use of coatings for dental implants is the

molecular grafting or chemical treatment of implant or coating surfaces to enhance cell adhesion and promote mineralization, and the production of matrix and marker proteins.

Proteins used for molecular grafting are present in the extracellular matrix, and implant surfaces that have been functionalized with fibronectin (FN), vitronectin (VN), or laminin (LN), to name a few [66]. Signaling Domains composed of several amino acids; are present along the chain of the extracellular matrix proteins and are the ones that interact with cell-membrane receptors. Example is Arg-Gly-Asp (RGD), the signaling domain derived from FN and LN. However, other sequences such as Tyr-Ile-Gly-Ser-Arg (YIGSR) or Arg-Glu- Asp-Val (REDV) have also been used [67-69].

Approaches used to functionalize Ti surface with different molecules, from adsorption (physical or chemical) to the use of covalent bonding or self-organized layers [],are immersion of the material in a solution containing the desired molecules in order to promote adsorption on the surface, Covalent bonding using, linker molecules can promote stronger adhesion to the implant are used to attach proteins, signaling domains [70-72], antibiotics [73], and growth factors such as human epidermal growth factor or recombinant human bone morphogenetic protein-2 to Ti and TiO2 surfaces [74,75]

3. Surface topography of dental implants

It has long been recognized that the chemical and morphological characteristics of implant

surfaces affect the behavior of the surrounding tissues. The ability of the implants to support bone formation can be enhanced by modifying surface topography [76-79]. The topography of the implant surfaces can now be manipulated at a wide range of length scales, down to the nano level. Several implant designs use surfaces with large pores to promote bone ingrowth and favorable anchoring. Previous analysis indicated that these pores have to be of the order of 100 µm and larger to allow for bone ingrowth. These can be fabricated using partial sintering of metal particles or spheres on the surface.

Texturing of the implant surface at the micro level has been proposed as a feasible alternative to promote bone apposition. Different techniques to increase the surface roughness, including sandblasting, grinding, Ti plasma spraying, or laser texturing [80, 64, 81] It could be argued that the main advantage of microtextured surfaces is the contribution to mechanical interlocking and tissue attachment of the implant. It should also be noted that implants with surfaces too rough have a high possibility of peri-implantitis and that the roughness will affect the degree of hydrophilicity. This effect could be described using Wentzel equation $\cos\theta r = r \cos\theta$ (where θr is the macroscopic contact angle on the rough surface, θ is the true contact angle, and r is a ratio between actual and apparent area, $r \geq 1$) [82]. Notice that according to this equation, for $\theta < 90°$ as can be expected for Ti-alloy surfaces, roughness tends to decrease the contact angle (increase hydrophilicity). This simple model shows how roughness can be playing an effect at multiple levels [83].

4. Nanocomposites for bone regeneration:

Ti and its alloys have had considerable advantages over other metals because of their inertness, which yields excellent biocompatibility and nonsensitization of tissues. Issues concerning the release of Ti and alloying elements from implants and the formation of Ti debris due to wear during implantation still remain. [84, 85]. Ceramic materials are known to have excellent aesthetics, corrosion resistance, and biocompatibility; several ceramic implants have been already commercialized. Unfortunately, in contrast to metallic materials, most ceramics suffer from almost a complete lack of plastic deformation; this

is due to the absence of mobile dislocation activity, although other modes of inelastic deformation, such as microcracking and in situ phase transformation, can provide limited alternative deformation mechanisms. The implications from this are that ceramics are inherently brittle.

Recently, it has been shown that a possible path to combining high strength and toughness in a ceramic material is to take advantage of the transformation toughening mechanisms in Nanozirconia-alumina materials [86,87]. These materials consist of a dispersion of a small amount of tetragonal ZrO2 particles (typically around 200 nm in size) in an Al2O3 matrix. The stress-induced phase transformation of metastable tetragonal grains toward monoclinic symmetry ahead of a propagating crack leads to a significant increase of the work of fracture. For the same pre-existing defects, these composites can work at loads two times higher than the pure materials without delayed failure. Hardness and stability are of prime interest in the dental field. Alumina-zirconia nanocomposites with relatively low zirconia content exhibit similar hardness values to alumina and are not susceptible to the hydrothermal instability [86-88].

The stabilization of the tetragonal zirconia phase in the nanocomposites is thought to arise from a combination of surface energy effects, constraints of the rigid matrix, and stabilizing oxide additions, e.g., yttria, such that transformation can occur locally once the constraints are removed, in this case when the crack propagates [89-92]. It is then necessary to develop processing methods that will allow the fabrication of materials in which the zirconia grains have controlled sub micronic size and are homogeneously dispersed in the ceramic matrix. Colloidal procedures in which a liquid precursor of the zirconia phase is mixed with the powders of the matrix ceramic phase present great potential. The use of a liquid precursor allows a more intimate mixing and a more homogeneous distribution of nanoparticles, avoiding the formation of aggregates after the heat treatment [93].

Alumina/zirconia nanocomposites offer an example of how nanotechnology offers an attractive path to the development of new implant materials but ceramics, even nanocomposite ceramics, will not replicate the unique combinations of mechanical properties of tooth tissues as they are, for example, much stiffer and wear-resistant. A possibility is to develop new hybrid organic/inorganic materials whose properties will closely match those of the tissue for which they substitute. Current hybrid organic/inorganic composites have significant problems related mostly to their mechanical performance and their degradation in vivo [94-95].

The tissues in teeth have very specific and sophisticated hierarchical architectures, withvstrength and toughening mechanisms built in at almost every dimension. Nano dimension is only one of them but we need to develop new technologies for the fabrication of materials with architectures designed at multiple length scales that, from the mechanical point of view, will exhibit extrinsic toughening mechanisms similar to those observed in natural composites. Recent advances in the processing of bio inspired materials may open new possibilities. In our laboratory we have pioneered a new technique, freeze casting, that can be used to fabricate ceramic-based composites with complex architectures to assemble novel, bio inspired hierarchical structures modeled after natural composites such as bone or nacre, striking a balance between mechanical and functional responses [96-97] This technique uses the controlled freezing of ceramic suspensions to generate porous ceramic scaffolds whose architecture is templated by the ice crystals. By controlling the composition of the suspension and the freezing conditions, it is possible to generate materials with complex hierarchical architectures that mimic those of the inorganic component of nacre at multiple length scales, from the nano to the macro levels. These scaffolds can subsequently be infiltrated with a second “soft” phase (e.g., polymer) to prepare composites that exhibit unique combinations of strength and toughness. In particular, it is possible to reach fracture resistance up to 300 times larger (in terms of energy) than that of their main ceramic constituents. As with natural materials, these values are much larger than what could be expected using the simple mixture of their components.

Conclusions

Nanoscale modification can alter the chemistry and/or topography of the implant surface. Different methods have been described to modify or to embellish titanium substrates with nanoscale features. Such changes alter the implant surface interaction with ions, biomolecules and cells. These interactions can favorably influence molecular and cellular activities and alter the process of osseointegration. Cell culture studies reveal that there exists a range of nanoscale topography that promotes the osteoinductive molecular program for

adherent osteoprogenitor cells. Additionally, nanoscale alterations may promote bone bonding behavior at the titanium bone interface. Nanoscale modification of titanium endosseous implant surfaces enhances interfacial bone formation measured as bone-to-implant contact. At this moment, both a hydrofluoric acid modified titanium endosseous implant with nanoscale features and two calcium phosphate nano feature-modified titanium implants are available for clinical use. The potential risks and benefits of manipulating biomaterial interfaces at the nanoscale will be defined by long-term clinical evaluation of such endosseous devices.

References

1. Branemark PI, Adell R, Breine U, Hansson BO, Lindstro¨m J, Ohlsson A. Intraosseous anchorage of dental prostheses. I. Experimental studies. Scand J Plast Reconstr Surg 1969;3:81–100.
2. Linder L, Albrektsson T, Brånemark PI, Hansson HA, Ivarsson B, Jo¨nsson U, et al. Electron microscopic analysis of the bone–titanium interface. Acta Orthop Scand 1983;54:45–52.
3. Albrektsson T, Sennerby L. Direct bone anchorage of oral implants: clinical and experimental considerations of the concept of osseointegration. Int J Prosthodont 1990;3:30–41.
4. Pye AD, Lockhart DEA, Dawson MP, Murray CA, Smith AJ. A review of dental implants and infection. Journal of Hospital Infection. 2009; 72(2):104–110. [PubMed: 19329223]
5. Christenson EM, Anseth KS, van den Beucken LJJP, Chan CK, Ercan B, Jansen JA, Laurencin CT, Li WJ, Murugan R, Nair LS, Ramakrishna S, Tuan RS, Webster TJ, Mikos AG. Nanobiomaterial applications in orthopedics. Journal of Orthopaedic Research. 2007; 25(1):11–22. [PubMed: 17048259]
6. Morton D, Jaffin R, Weber HP. Immediate restoration and loading of dental implants: clinical considerations and protocols. Int J Oral Maxillofac Implants 2004;19(Suppl.):103–8.
7. Coelho PG, Granjeiro JM, Romanos GE, Suzuki M, Silva NRF, Cardaropoli G, Thompson VP, Lemons JE. Basic Research Methods and Current Trends of Dental Implant Surfaces. Journal of Biomedical Materials Research Part B-Applied Biomaterials. 2009; 88B(2):579–596.
8. Albrektsson T,Wennerberg A. Oral implant surfaces: part 1 – review focusing on topographic and chemical properties of different surfaces and in vivo responses to them. Int J Prosthodont 2004;17:536–43.
9. Boyan BD, Lohmann CH, Dean DD, Sylvia VL, Cochran DL, Schwartz Z. Mechanisms involved in osteoblast response to implant surface morphology. Annual Review of Materials Research. 2001; 31:357–371.
10. Kasemo B. Biological surface science. Surface Science. 2002; 500:656–677.
11. Hench LL. Bioceramics. Journal of the American Ceramic Society. 1998; 81(7):1705–1728. [Review].
12. Hench, LL.; Andersson, O. Bioactive Glasses. In: Hench, LL.; Wilson, J., editors. An Introduction to Bioceramics. World Scientific; Singapore: 1993. p. 41-62.
13. Hench LL, Xynos ID, Polak JM. Bioactive glasses for in situ tissue regeneration. Journal of Biomaterials Science (Polymer). 2004; 15(4):543–562. [Review].
14. de Groot K. Medical Applications of Calciumphosphate Bioceramics. The Centennial Memorial Issue of the Ceramic Society of Japan. 1991; 99(10):943–953.
15. Filiaggi M, Pilliar R, Coombs N. Post-plasma spraying heat treatment of the HA coating/ Ti-6Al-4V implant system. J Biomed Mater Res. 1993; 27:191–198. [PubMed: 8436575]
16. Whitehead RY, Lacefield WR, Lucas LC. Structure and integrity of a plasma sprayed hydroxylapatite coating on titanium. Journal of Biomedical Materials Research. 1993; 27(12): 1501–7. [PubMed: 8113237].
17. Whitehead RY, Lucas LC, Lacefield WR. The effect of dissolution on plasma sprayed hydroxylapatite coatings on titanium. Clin Mater. 1993; 12(1):31–9. [PubMed: 10171675]
18. Porter AE, Botelho CM, Lopes MA, Santos JD, Best SM, Bonfield W. Ultrastructural comparison of dissolution and apatite precipitation on hydroxyapatite and silicon-substituted hydroxyapatite in vitro and in vivo. Journal of Biomedical Materials Research Part A. 2004; 69A(4):670–679. [PubMed: 15162409]

19. Porter AE, Hobbs LW, Rosen VB, Spector M. The ultrastructure of the plasma-sprayed hydroxyapatite-bone interface predisposing to bone bonding. Biomaterials. 2002; 23(3):725–733. [PubMed: 11771693]
20. Hench LL. Biomaterials: a forecast for the future. Biomaterials. 1998; 19(16):1419–1423. [PubMed: 9794512]
21. Costerton JW, Lewandowski Z, Caldwell DE, Korber DR, Lappinscott HM. Microbial Biofilms. Annual Review of Microbiology. 1995; 49:711–745. [Review].
22. Lincoff AM, Topol EJ, Ellis SG. Local drug delivery for the prevention of restenosis - fact, fancy, and future. Circulation. 1994; 90(4):2070–2084. [Review]. [PubMed: 7923695]
23. Riessen R, Isner JM. Prospectsfor site-specific delivery of pharmacologic and molecular therapies. Journal of the American College of Cardiology. 1994; 23(5):1234–1244. [Review]. [PubMed: 8144794]
24. Camenzind E, Bakker WH, Reijs A, Vangeijlswijk IM, Foley D, Krenning EP, Roelandt J, Serruys PW. Site-Specific Intravascular Administration Of Drugs - History Of A Method Applicable In Humans. Catheterization & Cardiovascular Diagnosis. 1997; 41(3):342–347. [PubMed: 9213034]
25. Lambert CR, Camenzind E, Robinson K. Local Drug Delivery. Catheterization & Cardiovascular Diagnosis. 1997; 41(3):231. [PubMed: 9213019]
26. Frenkel SR, Simon J, Alexander H, Dennis M, Ricci JL. Osseointegration on metallic implant surfaces: effects of microgeometry and growth factor treatment. J Biomed Mater Res. 2002; 63(6):706–713. [PubMed: 12418014]
27. Hunziker EB, Rosenberg LC. Repair of partial-thickness defects in articular cartilage: cell recruitment from the synovial membrane. J Bone Joint Surg Am. 1996; 78:721–733. [PubMed:8642029]
28. Tisdel CL, Goldberg VM, Parr JA, Bensusan JS, Staikoff LS, Stevenson S. The influence of a hydroxyapatite and tricalcium-phosphate coating on bone growth into titanium fiber-metal implants. Journal of Bone and Joint Surgery American Volume. 1994; 76(2):159–71.
29. Ducheyne, P.; Healy, K. Bioceramics. 1st International Bioceramics Symposium; Kyoto, Japan: Ishiyaku EuroAmerica Inc; 1988.
30. Chae JC, Collier JP, Mayor MB, Surprenant VA, Dauphinais LA. Enhanced ingrowth of porouscoated CoCr implants plasma-sprayed with tricalcium phosphate. Journal of Biomedical Materials Research. 1992; 26(1):93–102. [PubMed: 1577838]
31. Soballe K, Overgaard S, Hansen ES, Brokstedt-Rasmussen H, Lind M, Bunger C. A review of ceramic coatings for implant fixation. Journal of Long-Term Effects of Medical Implants. 1999; 9(1–2):131–151. [PubMed: 10537585]
32. Wheeler DL, Campbell AA, Graff GL, Miller GJ. Histological and biomechanical evaluation of calcium phosphate coatings applied through surface-induced mineralization to porous titanium implants. Journal of Biomedical Materials Research. 1997; 34(4):539–43. [PubMed: 9054537]
33. Willmann G. Coating of implants with hydroxyapatite material connections between bone and metal. Advanced Engineering Materials. 1999; 1(2):95–105. [Review].
34. Knowles JC, Gross K, Berndt CC, Bonfield W. Structural changes of thermally sprayed hydroxyapatite investigated by Rietveld analysis. Biomaterials. 1996; 17(6):639–45. [PubMed: 8652783]
35. McPherson R, Gane N, Bastow TJ. Structural characterization of plasma sprayed hydroxylapatite coatings. Journal of Materials Science: Materials in Medicine. 1995; 6:327–334.
36. Frayssinet P, Tourenne F, Primout I, Delga C, Sergent E, Besse C, Conte P, Guilhem A. A study of structure and degradation of nonpolymeric biomaterials implanted in bone using reflected and transmitted light microscopy. Biotechnic and Histochemistry. 1993; 68(6):333–41. [PubMed: 8292657]
37. Huaxia J, Ponton C, Marquis P. Microstructural characterization of hydroxyapatite coating on titanium. Journal of Materials Science: Materials in Medicine. 1992; 3:283–287.

38. Weinlaender M, Beumer J, Kenney EB, Moy PK, Adar F. Raman microprobe investigation of the calcium phosphate phases of three commercially available plasma-flame-sprayed hydroxyapatitecoated dental implants. Journal of Materials Science: Materials in Medicine. 1992; 3:397–40.
39. Zyman Z, Weng J, Liu X, Li X, Zhang X. Phase and structural changes in hydroxyapatite coatings under heat treatment. Biomaterials. 1994; 15(2):151–5. [PubMed: 8011862]
40. Gross KA, Berndt CC, Goldschlag DD, Iacono VJ. In Vitro Changes of Hydroxyapatite Coatings.International Journal of Oral & Maxillofacial Implants. 1997; 12(5):589–597. [PubMed: 9337018]
41. Hench LL. Bioceramics -from Concept to Clinic. Journal of the American Ceramic Society. 1991; 74(7):1487–1510.
42. Bloebaum RD, Beeks D, Dorr LD, Savory CG, DuPont JA, Hofmann AA. Complications with hydroxyapatite particulate separation in total hip arthroplasty. Clinical Orthopaedics and Related Research. 1994; 15(298):19–26. [PubMed: 8118974]
43. Koeneman J, Lemons J, Ducheyne P, Lacefield W, Magee F, Calahan T, Kay J. Workshop On Characterization of Calcium Phosphate Materials. Journal of Applied Biomaterials. 1990; 1:79–90
44. Lacefield, W. Hydroxylapatite Coatings. In: Hench, LaJW., editor. An Introduction to Bioceramics. World Scientific; Singapore: 1993. p. 223-238.
45. Gross KA, Gross V, Berndt CC. Thermal analysis of amorphous phases in hydroxyapatite coating. Journal of the American Ceramic Society. 1998; 81(1):106–12.
46. Suk-Woo H, Rber R, Eckert KL, Petitmermet M, Mayer J, Wintermantel E, Baerlocher C, Gruner H. Chemical and morphological changes of vacuum-plasma-sprayed hydroxyapatite coatings during immersion in simulated physiological solutions. Journal of the American Ceramic Society. 1998; 81(1):81–8.
47. Chen TS, Lacefield WR. Crystallization of ion beam deposited calcium phosphate coatings. Journal of Materials Research. 1994; 9(5):1284–90.
48. Wang BC, Chang E, Lee TM, Yang CY. Changes in phases and crystallinity of plasma-sprayed hydroxyapatite coatings under heat treatment: a quantitative study. Journal of Biomedical Materials Research. 1995; 29(12):1483–92. [PubMed: 8600138]
49. Chen J, Tong W, Cao Y, Feng J, Zhang X. Effect of atmosphere on phase transformation in plasma-sprayed hydroxyapatite coatings during heat treatment. Journal of Biomedical Materials Research. 1997; 34(1):15–20. [PubMed: 8978648]
50. Shirkhanzadeh M, Azadegan M, Stack V, Schreyer S. Fabrication of pure hydroxyapatite and fluoridated-hydroxyapatite coatings by electrocrystallisation. Materials Letters. 1994; 18(4):211– 14.
51. Tong W, Chen J, Cao Y, Lu L, Feng J, Zhang X. Effect of water vapor pressure and temperature on the amorphous-to-crystalline HA conversion during heat treatment of HA coatings. Journal of Biomedical Materials Research. 1997; 36(2):242–5. [PubMed: 9261686]
52. Wen HB, de Wijn JR, Cui FZ, de Groot K. Preparation of calcium phosphate coatings on titanium implant materials by simple chemistry. Journal of Biomedical Materials Research. 1998; 41(2):227–36. [PubMed: 9638527]
53. Koch B, Wolke JG, de Groot K. X-ray diffraction studies on plasma-sprayed calcium phosphatecoated implants. Journal of Biomedical Materials Research. 1990; 24(6):655–67. [PubMed: 2361962]
54. Ogiso M, Yamashita Y, Matsumoto T. Differences in microstructural characteristics of dense HA and HA coating. Journal of Biomedical Materials Research. 1998; 41(2):296–303. [PubMed: 9638535]
55. Radin S, Ducheyne P, Falaize S, Hammond A. In vitro transformation of bioactive glass granules into Ca-P shells. Journal of Biomedical Materials Research. 2000; 49(2):264–272. [PubMed: 10571915]
56. Evans SL, Gregson PJ. The effect of a plasma-sprayed hydroxyapatite coating on the fatigue properties of Ti-6Al-4V. Materials Letters. 1993; 16(5):270–4.

57. Lusquinos F, De Carlos A, Pou J, Arias JL, Boutinguiza M, Leon B, Perez-Amor M, Driessens FCM, Hing K, Gibson I, Best S, Bonfield W. Calcium phosphate coatings obtained by Nd : YAG laser cladding: Physicochemical and biologic properties. Journal of Biomedical Materials Research Part A. 2003; 64A(4):630–637. [PubMed: 12601774]
58. Lusquinos F, Pou J, Arias JL, Boutinguiza M, Leon B, Perez-Amor M, Driessens FCM, Merry JC, Gibson I, Best S, Bonfield W. Production of calcium phosphate coatings on Ti6Al4V obtained by Nd : yttrium-aluminum-garnet laser cladding. Journal of Applied Physics. 2001; 90(8):4231–4236.
59. Chai CS, Gross KA, Ben-Nissan B. Critical ageing of hydroxyapatite sol-gel solutions. Biomaterials. 1998; 19(24):2291–2296. [PubMed: 9884042]
60. Haddow DB, James PF, Van Noort R. Sol-gel derived calcium phosphate coatings for biomedical applications. Journal of Sol-Gel Science & Technology. 1998; 13(1–3):261–265.
61. Mardare CC, Mardare AI, Fernandes JRF, Joanni E, Pina SCA, Fernandes MHV, Correia RN. Deposition of bioactive glass-ceramic thin-films by RF magnetron sputtering. Journal of the European Ceramic Society. 2003; 23(7):1027–1030.
62. Zhitomirsky D, Roether JA, Boccaccini AR, Zhitomirsky I. Electrophoretic deposition of bioactive glass/polymer composite coatings with and without HA nanoparticle inclusions for biomedical applications. Journal of Materials Processing Technology. 2009; 209(4):1853–1860.
63. Tomsia AP, Saiz E, Song J, Bertozzi CR. Biomimetic bonelike composites and novel bioactive glass coatings. Advanced Engineering Materials. 2005; 7(11):999–1004.
64. Le, Guehennec L.; Soueidan, A.; Layrolle, P.; Amouriq, Y. Surface treatments of titanium dental implants for rapid osseointegration. Dental Materials. 2007; 23(7):844–854. [PubMed:16904738]
65. Frauchiger VM, Schlottig F, Gasser B, Textor M. Anodic plasma-chemical treatment of CP titanium surfaces for biomedical applications. Biomaterials. 2004; 25(4):593–606. [PubMed: 14607497]
66. Shin H, Jo S, Mikos AG. Biomimetic materials for tissue engineering. Biomaterials. 2003; 24(24):4353–4364. [PubMed: 12922148]
67. Shin HY, Bizios R, Gerritsen ME. Cyclic pressure modulates endothelial barrier function. Endothelium: Journal of EndothelialCell Research. 2003; 10(3):179–187.
68. Davis DH, Giannoulis CS, Johnson RW, Desai TA. Immobilization of RGD to < 111 > silicon surfaces for enhanced cell adhesion and proliferation. Biomaterials. 2002; 23(19):4019–4027. [PubMed: 12162335]
69. Massia SP, Hubbell JA. Covalent Surface Immobilization of Arg-Gly-Asp-Containing and Tyr- Ile-Gly-Ser-Arg-Containing Peptides to Obtain Well-Defined Cell-Adhesive Substrates. Analytical Biochemistry. 1990; 187(2):292–301. [PubMed: 2382830]
70. Beutner R, Michael J, Schwenzer B, Scharnweber D. Biological nano-functionalization of titanium-based biomaterial surfaces: a flexible toolbox. Journal of the Royal Society Interface. 2010; 7:S93–S105.
71. Schliephake H, Scharnweber D. Chemical and biological functionalization of titanium for dental implants. Journal of Materials Chemistry. 2008; 18(21):2404–2414.
72. Schliephake H, Scharnweber D, Dard M, Sewing A, Aref A, Roessler S. Functionalization of dental implant surfaces using adhesion molecules. Journal of Biomedical Materials Research Part B-Applied Biomaterials. 2005; 73B(1):88–96.
73. Jose B, Antoci V, Zeiger AR, Wickstrom E, Hickok NJ. Vancomycin covalently bonded to titanium beads kills Staphylococcus aureus. Chemistry & Biology. 2005; 12(9):1041–1048. [PubMed: 16183028]
74. Lange K, Herold M, Scheideler L, Geis-Gerstorfer J, Wendel HP, Gauglitz G. Investigation of initial pellicle formation on modified titanium dioxide (TiO2) surfaces by reflectometric interference spectroscopy (RIfS) in a model system. Dental Materials. 2004; 20(9):814–822. [PubMed: 15451236]

75. Becker J, Kirsch A, Schwarz F, Chatzinikolaidou M, Rothamel D, Lekovic V, Laub M, Jennissen HP. Bone apposition to titanium implants biocoated with recombinant human bone morphogenetic protein 2 (rhBMP-2). A pilot study in dogs (vol 10, pg 217, 2006). Clinical Oral Investigations. 2006; 10(3):225–225.
76. Healy, K.; Harbers, G.; Barber, T.; Sumner, D. Osteoblast Interactions with Engineered Surfaces. In: Davies, JE., editor. Bone Engineering. Em Squared Incorporated; Toronto, Canada: 2000. p. 268-281.
77. Boyan, B.; Schwartz, Z. Modulation of Osteogenesis via Implant Surface Design. In: Davies, JE., editor. Bone Engineering. Em Squared Incorporated; Toronto, Canada: 2000. p. 232-239.
78. Lemons, J. Structure of Bone Adjacent to Different Dental Implants. In: Davies, JE., editor. Bone Engineering. Em Squared Incorporated; Toronto, Canada: 2000. p. 313-320.
79. Ricci, JL.; Charvet, J.; Frenkel, SR.; Chang, R.; Nadkarni, P.; Turner, J.; Alexander, H. Bone response to laser microtextured surfaces. In: Davies, JE., editor. Bone Engineering. em squared incorporated; Toronto: 2000. p. 282-294.
80. Buser D, Schenk RK, Steinemann S, Fiorellini JP, Fox CH, Stich H. Influence of surface characteristics on bone integration of titanium implants. A histomorphometric study in miniature pigs. Journal of Biomedical Materials Research. 1991; 25(7):889–902. [see comments]. [PubMed: 1918105]
81. Simmons CA, Valiquette N, Pilliar RM. Osseointegration of sintered porous-surfaced and plasma spray-coated implants: An animal model study of early postimplantation healing response and mechanical stability. Journal of Biomedical Materials Research. 1999; 47(2):127–138. [PubMed: 10449624]
82. Wenzel RN. Surface roughness and contact angle. Journal of Physical Chemistry. 1949; 53(9): 1466–1467.
83. Elias CN, Oshida Y, Lima JHC, Muller CA. Relationship between surface properties (roughness, wettability and morphology) of titanium and dental implant removal torque. Journal of the Mechanical Behavior of Biomedical Materials. 2008; 1(3):234–242. [PubMed: 19627788]
84. Li Y, Wong C, Xiong J, Hodgson P, Wen C. Cytotoxicity of Titanium and Titanium Alloying Elements. Journal of Dental Research. 2010; 89(5):493–497. [PubMed: 20332331]
85. Costa MT, Lenza MA, Gosch CS, Costa I, Ribeiro-Dias F. In vitro evaluation of corrosion and cytotoxicity of orthodontic brackets. Journal of Dental Research. 2007; 86(5):441–445. [PubMed: 17452565]
86. Deville S, Chevalier J, Fantozzi G, Bartolome JF, Requena J, Moya JS, Torrecillas R, Diaz LA. Low-temperature ageing of zirconia-toughened alumina ceramics and its implication in biomedical implants. Journal of the European Ceramic Society. 2003; 23(15):2975–2982.
87. Pecharroman C, Bartolome JF, Requena J, Moya JS, Deville S, Chevalier J, Fantozzi G, Torrecillas R. Percolative mechanism of aging in zirconia-containing ceramics for medical applications. Advanced Materials. 2003; 15(6):507–511.
88. Chevalier J, Gremillard L, Deville S. Low-temperature degradation of Zirconia and implications for biomedicalimplants. Annual Review of Materials Research. 2007; 37:1–32.
89. De Aza AH, Chevalier J, Fantozzi G, Schehl M, Torrecillas R. Crack growth resistance of alumina, zirconia and zirconia toughened alumina ceramics for joint prostheses. Biomaterials. 2002; 23(3):937–945. [PubMed: 11774853]
90. Ruhle M, Claussen N, Heuer AH. Transformation and Microcrack Toughening as Complementary Processes in Zro2-Toughened Al2o3. Journal of the American Ceramic Society. 1986; 69(3):195–197.
91. Heuer A, Claussen N, Kriven WM, Ruhle M. Stability of Tetragonal Zro2 Particles in Ceramic Matrices. Journal of the American Ceramic Society. 1982; 65(12):642–650.
92. Kibbel B, Heuer AH, Ruhle M. Transformation Zones in Zirconia-Toughened Alumina. American Ceramic Society Bulletin. 1982; 61(8):812–812.
93. Schehl M, Diaz LA, Torrecillas R. Alumina nanocomposites from powder-alkoxide mixtures. Acta Materialia. 2002; 50(5):1125–1139.

94. Russias J, Saiz E, Nalla RK, Gryn K, Ritchie RO, Tomsia AP. Fabrication and mechanical properties of PLA/HA composites: A study of in vitro degradation. Materials Science & Engineering C-Biomimetic and Supramolecular Systems. 2006; 26(8):1289–1295.
95. Neuendorf RE, Saiz E, Tomsia AP, Ritchie RO. Adhesion between biodegradable polymers and hydroxyapatite: Relevance to synthetic bone-like materials and tissue engineering scaffolds. Acta Biomaterialia. 2008; 4(5):1288–1296. [PubMed: 18485842]
96. Deville S, Saiz E, Tomsia AP. Freeze casting of hydroxyapatite scaffolds for bone tissue engineering. Biomaterials. 2006; 27(32):5480–5489. [PubMed: 16857254]
97. Deville S, Saiz E, Nalla RK, Tomsia AP. Freezing as a path to build complex composites. Science. 2006; 311(5760):515–518. [PubMed: 16439659]