International Journal of Applied Dental Sciences 2018; 4(2): 149-153

ISSN Print: 2394-7489
ISSN Online: 2394-7497
IJADS 2018; 4(2): 149-153

www.oraljournal.com
Received: 08-02-2018
Accepted: 12-03-2018

Dr. Shraddha Rathi
Assistant Professor, Department of Prosthodontics, Dr. Z.A. Dental College, Aligarh Muslim University (AMU) Campus, Aligarh, Uttar Pradesh, India

Dr. Ankit Verma
Resident, Department of Prosthodontics, Dr. Z.A. Dental College, Aligarh Muslim University (AMU) Campus, Aligarh, Uttar Pradesh, India

Correspondence
Dr. Ankit Verma
Resident, Department of Prosthodontics, Dr. Z.A. Dental College, Aligarh Muslim University (AMU) Campus, Aligarh, Uttar Pradesh, India

Nanoscale modifications of dental implants: An emerging trend

Dr. Shraddha Rathi and Dr. Ankit Verma

Abstract
Recent advancements in engineering tools and techniques coupled with the extrapolation of nanotechnology in the field of dental implant science have rendered incorporation of nano scale features on dental implant surfaces feasible. Most of the nature's biological process, including bone formation occur at nanoscale levels, so this endeavour is basically an attempt to mimic the nature's nano science in order to achieve better osseointegration levels and higher implant success rates. Such nano-modified implants in addition to macro- and micro-scale features also have nano features incorporated within the micro-topography.Several methods have been developed to incorporate nano scale features within the micro-topography of implant surface and dental implants possessing such combination features have now been made commercially available.

Keywords: nanotopography, microtopography, contact guidance, discrete crystalline deposition, ion beam assisted deposition, laser ablation

Introduction
Nanotechnology has been defined as the science and engineering involved in the design, synthesis, characterization and application of materials and devices whose smallest functional organization, in at least one dimension is on the nanometer scale [1]. The National Nanotechnology initiative in US has ascertained the scale range of nanotechnology as 1 to 100 nanometers. The basic principle governing this technology has its root in the science of quantum mechanics, and to be more specific, quantum size effect on matter. The quantum size effect describes the physics of electron properties in solids with great reductions in particle size [2]. This effect begin to dominate the behaviour of the matter as soon as the size approaches the nanoscale range and subsequently the matter exhibit substantial departures from the property of their bulk materials. That is to say, materials reduced to nanoscale size might display entirely different properties from their bulk materials. It happens because the properties of any bulk material are the average of all the quantum forces of all the atoms that constitute the material, but as the size of the material is gradually diminished to the nanoscale level specific behaviour of the individual atoms or molecules comes into play; which may be entirely different when such individual atoms or molecules were aggregated to form the bulk material.

Nanotechnology has found a wide range of applications in health and medicine and the concept has also extrapolated to the field of dental implant science. It has been discovered that while microscale topography of implant surface influences osseointegration at cellular level, nanoscale topography influences osseointegration at both molecular and cellular level. Nano-scale modifications of implant surface exhibit alteration not only in surface topography but also in chemical properties. Cell responses differ depending upon topography and surface chemistry, and thus by controlling these parameters it becomes possible to target specific cellular response and modulate them in such a manner that higher level of osseointegration is attained. Nowadays, a great variety of methods to incorporate nanoscale features on the dental implant surfaces have been developed and several dental implants possessing these features are commercially available in market.

Rationale & biological basis
Most of the nature's biological process including bone formation occur at nanoscale levels,

which has been attributed at least in part to the ability of the living cells to interact with nanometric extracellular features. This biological effect is mediated by transmembrane receptor protein called integrins. The integrins have ligand binding sites in their extracellular domains that binds to specific peptide sequence of extracellular proteins. An example of such peptide sequence is arginine-glycine-asparatic acid (RGD) present in extracellular protein like fibronectin and vitronectin. The cystolic domain of the integrins bind to a large number of proteins such as paxillin or zyxin either directly or via scaffolding proteins [3]. These proteins are found to have a role in the intracellular signalling via mechano-transduction pathway that ultimately brings about the desired cell response. Following the placement of dental implant at the osteotomy site, blood is invariably the first tissue that comes in contact with its surface. Blood contains over 200 proteins and it leads to deposition of protein monolayer on the implant surface[4]. Composition of this protein monolayer is largely governed by topography and chemical properties of the implant surface. Nanoscale modifications of the implant surface may favourably alter the topography and chemistry of the implant surface. It needs to be emphasized that proteins are charged molecules that change conformation (i.e. the protein's 3D shape) depending upon their electro-chemical environment. Therefore surface charge characterestics of the implant are thought to determine a protein's conformation which in turn is determined by surface chemistry of implants. The conformation of the protein is important as it determines whether certain bioactive peptide sequences located within the protein will be available for the incoming cells [4]. Also, Protein molecules have sizes in order of nano-meters (10^{-9}m). Therefore nano-irregulaties/ structures on the implant surface will provide effective surface for proteins to interact, configure and bind. Webster *et al*. [5] in their study showed increased vitronectin deposition on nanophase alumina, titania and hydroxypatite than it was on the conventional surfaces of the same ceramics. This resulted in greater osteoblastic adhesion on these nanophase materials compared to their conventional surfaces.

Stem cells are a class of undifferentiated cells that are capable of self-renewal (producing copies of themselves) and has the potential to differentiate into specialized cell types depending upon their biophysical and biochemical microenvironment. Human mesenchymal stem cells (hMSCs) can give rise to multiple cell lineages (adipocytes, myoblasts, osteoblasts) depending upon the extracellular micro-environment. Runt-related transcription factor 2 (RUNX2), also called Cbfa1 is the master gene necessary for osteoblast lineage commitment [6]. Bone morphogenic protein 2 (BMP-2) induces expression of Osx transcription factor independent of RUNX2 [7]. Osx is involved in the differentiation step from pre-osteoblast to mature osteoblast and induces osteocalcin expression [8]. Osteocalcin is expressed only by fully differentiated osteoblasts [9]. Type I collagen (COLL-1) is expressed in high levels in the early synthetic phase to support the proliferating cells [10] but its expression gradually declines as the cell matures [11]. Alkaline phosphatase (ALP) a membrane bound enzyme contained in the matrix vesicles that contributes to making the extracellular matrix competent for mineralization [10]. It is considered an early marker of osteoblast differentiation; hence, it expression increases during extracellular matrix maturation and decreases when mineralization is well progressed [12]. Living cells are remarkable in their ability to sense nano-structure and nanoscale surface modifications of dental implants have been shown to influence cellular behaviour. Flouride modification of titanium alters the surface oxide layer and creates a fluoride containing titanium oxide layer with a characteristic nanostructural surface topography [11]. Several studies have shown that Fluoride- modified titanium implant surface exhibit increased expression of RUNX2 [13, 14], OSX [14] and COLL-I [15] genes.

Contact guidance refers to the ability of the cells to orient, grow and organize along a substrate influenced by geometrical patterns such as nano-or micro-sized grooves. It has been found that when the dimensions of the grooves on a micro-textured or nano-textured surface are reduced to the sizes of the cells or less, cells become responsive to these geometrical cues. Osteoblasts like cells align along the nano-grooves for groove size wider than 75nm [16]. Fibroblasts align on grooves wider than 150nm [17]. In retrospect, too large values of groove widths can diminish the effects of contact guidance [18]. On certain groove width cell density, proliferation and synthesis show marked improvement. Commercially available Laser-Lok implants (Bio-horizons, Birmingham, AL, USA) processed by laser ablation technology to generate a pattern of micro-and nanoscale microchannels exploits the phenomenon of contact guidance. It has extremely consistent microchannels that are optimally sized to attach and organize both osteoblasts and fibroblasts.

Nano-modification methods

With the essence of macro-and micro-topographical features in relation to implant surface been very well established and market being flooded with such implants exhibiting both these features, the research paradigm in implant industry has now been shifting towards nano-modified implants. Such implants in addition to macro and micro-features also has nano features incorporated within the micro-topography. Research studies have shown that several industrial methods, both physical as well as chemical, can be employed to incorporate nano -scale features to dental implant surfaces. However, with the current state of technology only few of these methods have been considered economically viable from the point of view of commercial production.

Four novel implant surfaces presenting nano scale features have been produced and made commercially available. These include Nano Tite™ (Bicon LLC, Boston, USA), Nano Tite™ (Biomet 3i, Palm Beach Gardens, USA), OSSEAN™ (Intra-Lock International, Boca, Raton, FL, USA) and Osseo Speed™ (Astra Tech, AB, Mölndal, Sweden). Besides some of the implant surfaces like SLA active (Institut Straumann, Basel, Switzerland) and TiUnite (Nobel Biocare, Zurich, Switzerland) which were initially not developed with the intention of incorporating nano features, was discovered afterwards by scientific reports to actually possess these features [19].

The Bicon surface of Nano Tite™ is prepared by initially treating the implant surface by subtractive method (alumina blasting and acid etching) to obtain a moderately roughened micro-textured surface followed by an additive method in which 20-50nm thickness of amorphous calcium phosphate coating is deposited on it by ion beam-assisted deposition (IBAD) method. The rationale for depositing such thin film on the moderately roughened micro-textured surface was to exploit the bioactive nature of calcium phosphate and avoid long term complications due to fracture or delamination of thick calcium phosphate coatings deposited by conventional method. Due to the osteogenic potential of calcium phosphate, bone formation at the implant site will be hastened and at the

same time due to amorphous configuration of these coatings, they would be entirely dissolved from the surface leading to intimate contact between the bone and implant surface.

The Biomet 3i surface of NanoTite™ is also prepared by initially treating the implant surface by subtractive method (dual acid etching) to generate a micro-textured pattern following which a sol-gel process is performed called discrete crystalline deposition (DCD) for the deposition of nano-sized hydroxypatite crystals on the discrete regions of micro-textured implant surface. These crystals roughly make up 50% of total area of implant surface [20]. The rationale behind DCD method is to render a multiscale scale texturing to the implant surface (both micro- and nano-texture) in addition to the osteoconductive potential of hydroxypatite coating. The main advantage gained by this coating method is that since the hydroxypatite crystals are deposited on discrete rather continuous regions on the implant surface, the micro-topography generated by dual acid etching process remain unobliterated by the surface coat on at least half of the implant surface area.

The Ossean™ surface of Intra-Lock implant is manufactured by robotic micro-blasting of the implant surface with calcium phosphate powder that simultaneously results in nanometer scale topography within the larger scale micro-topography. A unique feature of this surface of ossean surface is the existence of fractal phenomenon i.e. to say they are characterized by a having a surface topography that is similar at all levels of magnification from macroscale to nano-scale. Calcium phosphate molecules (More than thousand times smaller than nanoparticles) have been found to be impregnated in the titanium oxide layer by AUGER spectroscopy which retain their bioactive activity and render the surface osteoconductive.

The Osseospeed™ surface is prepared by initially blasting the grade 4 titanium implant surface with TiO_2 particles to create micro-roughness and then treating it with dilute HF to generate nano-meter scale texturing. SEM investigations show that HF treatment reduces the roughness at micro-scale but it incorporates nano-scale features within the micro-topography.

The Ti Unite surface of Nobel Biocare dental implants is modified by Anodic Spark Dissolution (ASD) in an electrolyte bath containing phosphoric acid. This surface treatment results in thickened titanium oxide layer (up to 10 µm) and a moderately rough surface (R_a=1.2 µm) topography with micropores as well as nanopores[21]. Many Studies have also shown the presence of phosphorous in the oxide layer. Thus the enhanced osseointegration levels seen with Ti Unite surfaces compared to machined surfaces can be attributed to both its chemistry related factors as well as topographic factors.

The abbreviation SLA stands for sand blasted, large grit and acid etched and was introduced by Buser *et al*. in 1991. The surface is produced by large grit 250-500µm blasting process followed by etching with hydrochloric acid/sulfuric acid. Sand blasting generates macro roughness and acid etching leads to microtexture and cleaning [22, 23, 24]. SLA implant surface (Institut Straumann AG, Basel, Switzerland) is found to be highly osteoconductive[25] but one of its limitation is its hydrophobic nature [26]. A modified SLA surface with high hydrophilicity and surface free energy has been developed and made commercially available under trade name SL Active, (Institut Straumann AG, Basel Switzerland). The mod SLA surface are produced similarly like SLA surface, but after same sand blasting and acid etching procedure, the implants are rinsed in N_2 protection and directly stored in isotonic NaCl solution at pH 4-6, again protected by N_2 filling [27, 28]. The Na and Cl solutions shield the hydroxylated dioxide layer from contamination with hydrocarbons and carbons from the atmosphere thus preserving the hydrophilicity of the implant surface. Once the implant is placed, sodium and chloride ions easily dissociate from surface creating a creating a clean chemically active hydrophilic dioxide layer [27]. Though not explicitly labeled as a nano structured implant surface, studies have shown that the SLA ctive implant surface do exhibits elements of nanotopography.

Recent research trends have also been focused on coating the implant surface with metallic nano particles in an attempt to exploit their anti-microbial nature, thereby improving the overall success rate of implants by preventing bacterial infiltration and bio-film formation. In this regard, silver nano particles (SNPs) have received special attention. SNPs have higher anti-microbial potency than free silver ions [29] and their antimicrobial effect is attributed to their ability to adhere and induce gaps in the bacterial cell membrane ultimately leading to fragmentation of the cells [30]. They are effective in typically low doses over the implant surface which render them non- cytotoxic and biocompatible. Various techniques can be employed to impregnate the implant surface with SNPs. Zhang *et al*. [31] used Micro-arc oxidation (MAO) method to incorporate silver nano particles onto the porous TiO_2 coating on the implant surface. They proposed that their applied ion implantation method may act as a promising approach for producing bacterial resistant implant surfaces. Other metallic nano particles like CuO nanoparticles and ZnO nanoparticles are also being looked upon in this regard due to their potential anti-microbial effect.

Certain metallic nano particles have been found to possess osseointegrative capability. In this regard, gold nanoparticles (GNPs) deserve special mention. Heo *et al*. [32] in their study have shown that the gold nano particles immobilized on titanium implant surfaces significantly enhances the osteogenic differentiation with increased mRNA expression of osteogenic differentiation specific genes in human adipose-derived stem cells (ADSCs). *In vivo* results from their study also showed that GNPs coating had a significant influence on the osseous interface formation. They proposed that gold nanoparticles (GNPs) can serve as quite attractive materials for use as osteogenic agents due to their potential effects on the stimulation of osteoblast differentiation.

Evidences from the literature

Mendes *et al*. [33] in rat study models reported bone bonding between the DCD nanometer scale modified surface and bone. In a controlled study performed in human subjects DCD surface was compared to its dual acid etched precursor on histomorphometric basis by placing them in posterior maxilla followed by their retrieval after two months of healing. Higher BIC values were reported around DCD surface compared to its predecessor [34].

Marin *et al*. [35] compared Ossean surface and dual etched surfaces in a Beagle model. They reported that while no statistical differences in BIC was found between the two surfaces at both 2 and 4 weeks, a significantly increased torque removal value was reported for the Ossean surface suggesting that the bone formed around Ossean surface has higher mechanical properties. In another study performed in human subjects, the above mentioned two surfaces were compared by placing them in pairs in posterior maxilla.

Following the retrieval of implants after a period of 2 months, the histomorphometric evaluation showed significantly higher BIC and osteocyte density with the newly formed bone for the Ossean surface relative to the control [36].

In a comparative study performed by Ellingsen *et al.* [37] in rabbit tibia models, significantly higher removal torque values and sheer strength between the bone and the implants were measured for Osseospeed surfaces after 3 months relative to its micrometer scale predecessor (TiOblast, Astratech AB, Mölndal, Sweden). The histomorphometric evaluation also demonstrated higher BIC value for Osseospeed surface compared to its predecessor after 1 month. Rocci *et al.* [38] also performed a comparative study between the Osseospeed and TiOblast implant surfaces in human subjects. Histomorphometric analysis showed higher BIC value for Osseospeed surface compared to its predecessor after a period of two months.

Conclusions

The introduction of nanotechnology in dental implant manufacturing industry has opened a new avenue of nano scale characterization of dental implant enabling the implant surface to mimic the surface topography of extracellular matrix components of the natural tissue. This has provided a new insight into the science of osseointegration and has set a new trend in the implant surface modification techniques. Several dental implants are now commercially available claiming to possess such nano scale features. Comparative studies performed *in vitro* and *in vivo* pre-clinical models have shown superiority of the nanomodified surfaces to their predecessors. However, such comparative long clinical trials have been lacking from the literature. In absence of such randomized controlled trials (RCT), it cannot be ascertained that whether these nano scale modifications really have a significant clinical impact. Thus, more research work and long term clinical trials are warranted in this field in order to fully acknowledge its true potential.

References

1. Silva GA. Introduction to nanotechnology and its application to medicine. J Surg Neurol. 2004; 61:216-20.
2. Berger M. Preface In Nano-Society Pushing the Boundaries of Technology. RSC Publishing, Cambridge UK, 2009.
3. Bressan E, Sbricoli L, Guazzo R, Tocco I, Roman M, Vindigni V *et al*. Nanostructured Surfaces of Dental Implants. Int J Mol Sci. 2013; 14(1):1918-1931.
4. Ratner BD. New ideas in biomaterials science: A path to engineered biomaterials. J Biomed Mater Res. 1993; 27:837-50.
5. Webster TJ, Ergun C, Doremus RH, Siegel RW, Bizios R. Specific proteins mediate enhanced osteoblast adhesion on nanophase ceramics. J Biomed Mater Res. 2000; 51(3):475-83.
6. Ducy P, Zhang R, Geoffroy V, Ridall AL, Karsenty G. Osf2/Cbfa1: a transcriptional activator of osteoblast differentiation. Cell. 1997; 89(5):747-54.
7. Matsubara T, Kida K, Yamaguchi A, Hata K, Ichida F, Meguro H *et al*. BMP2 regulates osterix through Msx2 and Runx2 during osteoblast differentiation. J Biol. Chem. 2008; 283:29119-29125.
8. Tu Q, Valverde P, Chen J. Osterix enhances proliferation and osteogenic potential of bone marrow stromal cells. Biochem Biophys Res Commun. 2006; 341(4):1257-65.
9. Aubin JE. Advances in the osteoblast lineage. Biochem Cell Biol. 1998; 76(6):899-910.
10. Stein GS, Lian JB, Stein JL, Van Wijnen AJ, Montecino M. Transcriptional control of osteoblast growth and differentiation. Physiol Rev. 1996; 76(2):593-629.
11. Ellingsen JE, Monjo M, Ramis JM. Development of Novel Flouride-Modified Implant Surface for Clinical Use in Implant surfaces and their Biological and Clinical Impact. Wennerberg A, Albrektsson T, Jimbo R. Springer-Verlag Berlin Heidelberg, 2015, 45.
12. Kim IS, Song YM, Cho TH, Park YD, Lee KB, Noh I *et al*. *In vitro* response of primary human bone marrow stromal cells to recombinant human bone morphogenic protein-2 in the early and late stages of osteoblast differentiation. Dev Growth Differ. 2008; 50(7):553-64.
13. Isa ZM, Schneider GB, Zaharias R, Seabold D, Stanford CM. Effects of fluoride-modified titanium surfaces on osteoblast proliferation and gene expression. Int J Oral Maxillofac Implants. 2006; 21(2):203-11.
14. Guo J, Padilla RJ, Ambrose W, De Kok IJ, Cooper LF. The effect of hydrofluoric acid treatment of TiO2 grit blasted titanium implants on adherent osteoblast gene expression *in vitro* and *in vivo*. Biomaterials. 2007; 28(36):5418-25.
15. Guida L, Annunziata M, Rocci A, Contaldo M, Rullo R, Oliva A. Biological response of human bone marrow mesenchymal stem cells to fluoride-modified titanium surfaces. Clin Oral Implants Res. 2010; 21(11):1234-41.
16. Lamers E, Walboomers XF, Domanski M, te Riet J, van Delft FC, Luttge R *et al*. The influence of nanoscale grooved substrates on osteoblast behavior and extracellular matrix deposition. Biomaterials. 2010; 31(12):3307-16.
17. Loesberg WA, te Riet J, van Delft FC, Schön P, Figdor CG, Speller S *et al*. The threshold at which substrate nanogroove dimensions may influence fibroblast alignment and adhesion. Biomaterials. 2007; 28(27):3944-51.
18. Charest JL, García AJ, King WP. Myoblast alignment and differentiation on cell culture substrates with microscale topography and model chemistries. Biomaterials. 2007; 28(13):2202-10.
19. Wennerberg A, Galli S, Albrektsson T. Current knowledge about the hydrophilic and nanostructured SLActive surface. Clin Cosmet Investig Dent. 2011; 3:59-67.
20. Bonfante EA, Granato R, Marin C, Jimbo R, Giro G, Suzuki M *et al*. Biomechanical testing of microblasted, acid-etched/microblasted, anodized, and discrete crystalline deposition surfaces: an experimental study in beagle dogs. Int J Oral Maxillofac Implants. 2013; 28(1):136-42.
21. Sawase T, Watanabe I. Surface Modification of Titanium and its alloy by Anodic Oxidation for Dental Impant. In implant surfaces and their Biological and Clinical Impact. Wennerberg A, Albrektsson T, Jimbo R. Springer-Verlag Berlin Heidelberg, 2015, 67.
22. Orsini G, Assenza B, Scarano A, Piattelli M, Piattelli A. Surface analysis of machined versus sandblasted and acid-etched titanium implants. Int J Oral Maxillofac Implants. 2000; 15:779-84.
23. Klokkevold PR, Johnson P, Dadgostari S, Caputo A, Davies JE, Nishimura RD. Early endosseous integration enhanced by dual acid etching of titanium: a torque removal study in the rabbit. Clin Oral Implants Res. 2001; 12:350-7.

24. Galli C, Guizzardi S, Passeri G, Martini D, Tinti A, Mauro G *et al*. Comparison of human mandibular osteoblasts grown on two commercially available titanium implant surfaces. J Periodontol. 2005; 76:364-72.
25. Cochran DL, Schenk RK, Lussi A, Higginbottom FL, Buser D. Bone response to unloaded and loaded titanium implants with a sand blasted and acid etched surface: a istometric study in canine mandible. J Biomed Mater Res. 1998; 40(1):1-11
26. Rupp F, Scheideler L, Olshanska N, de Wild M, Wieland M, Geis-Gerstorfer J. Enhancing free surface energy and hydrophilicity through chemical modification of microstructured titanium implant surfaces. J Biomed Mater Res A. 2006; 76(2):323-34.
27. Zhao G, Schwartz Z, Wieland M, Rupp F, Geis-Gerstorfer J, Cochran DL *et al*. High surface energy enhances cell response to titanium substrate micro-structure. J Biomed Mater Res A. 2005; 74(1):49-58
28. Buser D, Broggini N, Weiland M, Schenk RK, Denzer AJ, Cochran DL *et al*. Enhanced bone apposition to a chemically modified SLA titanium surface. J Dent Res. 2004; 83(7):529-33.
29. Hamouda IM. Current perspectives of nanoparticles in medical and dental biomaterials. Journal of biomedical research. 2012; 26:143-51.
30. Maleki Dizaj S. Preparation and study of vitamin A palmitate microemulsion drug delivery system and investigation of co-surfactant effect. Journal of nanostructure in chemistry. 2013; 3:1-6.
31. Zhang P, Zhang Z, Li W. Antibacterial TiO2 coating incorporating silver nanoparticles by microarc oxidation and ion implantation. Journal of Nanomaterials. 2013; 2013:2.
32. Heo DN, Ko WK, Lee HR, Lee SJ, Lee D, Um SH *et al*. Titanium dental implants surface-immobilized with gold nanoparticles as osteoinductive agents for rapid osseointegration. J Colloid Interface Sci. 2016; 469:129-137.
33. Mendes VC, Moineddin R, Davies JE. The effect of discrete calcium phosphate nanocrystals on bone-bonding to titanium surfaces. Biomaterials. 2007; 28(32):4748-55.
34. Orsini G, Piattelli M, Scarano A, Petrone G, Kenealy J, Piattelli A *et al*. 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(2):209-18.
35. Marin C, Granato R, Suzuki M, Gil JN, Piattelli A, Coelho PG. Removal torque and histomorphometric evaluation of bioceramic grit-blasted/acid-etched and dual acid-etched implant surfaces: an experimental study in dogs. J Periodontol. 2008; 79(10):1942-9
36. Shibli JA, Grassi S, Piattelli A, Pecora GE, Ferrari DS, Onuma T *et al*. Histomorphometric evaluation of bioceramic molecular impregnated and dual acid-etched implant surfaces in the human posterior maxilla. Clin Implant Dent Relat Res. 2010; 12(4):281-8.
37. Ellingsen JE, Johansson CB, Wennerberg A, Holmén A. Improved retention and bone-tolmplant contact with fluoride-modified titanium implants. Int J Oral Maxillofac Implants. 2004; 19(5):659-66.
38. Rocci M, Rocci A, Martignoni M, Albrektsson T, Barlattani A, Gargari M. Comparing the TiOblast and Osseospeed surfaces. Histomorphometric and histological analysis in humans. Oral Implantol (Rome). 2008; 1(1):34-42.