



CURRENT BONE SUBSTITUTES IN IMPLANT DENTISTRY

Dental Science

K. Hemavarthini. B.D.S.*	Undergraduate student, Department of Prosthodontics, SRM Kattankulathur Dental College and Hospital, SRMIST ,Kattankulathur, Chennai- 603203, Tamilnadu state, India.*Corresponding Author
Thamarai Selvan KM M. D. S	Senior lecturer, Department of Prosthodontics, SRM Kattankulathur Dental College and Hospital, SRMIST ,Kattankulathur, Chennai- 603203, Tamilnadu state, India.
V. Vidya Shree Nandini M.D.S	Professor and Head, Department of Prosthodontics, SRM Kattankulathur Dental College and Hospital, SRMIST ,Kattankulathur, Chennai- 603203, Tamilnadu state, India.

ABSTRACT

Implant dentistry is becoming popular in contemporary world. Dental implants are good option for permanent prosthesis. For a standard dental implant placement, enough bone thickness is required. Many cases lack sufficient bone quality and quantity. Hence, the search for bone substitutes becomes necessary. Bone formation and repair is multifactorial that needs osteogenic cells, matrix of osteo-conductivity, signalling of osteo-inductivity, volume maintenance and balancing mechanical property and vascularization. In scientific application, for the reconstructive purposes such as bone repair and bone augmentation we use bone replacement substances. In recent times, the use of calcium phosphate as a primary bone substitute is increased substantially. These bone substitute differ in their composition, mechanical properties, maintenance of the volume, organic function and they have their own dis-advantages and advantages. The profound effect of biological and mechanical behaviour of calcium phosphate bone substitute is due to their intrinsic factors. The preference of the bone substitute is not an easy task and generally relies upon on the needs of application and also related to organic and the mechanical properties. It is not necessary that all bone graft substitutes have to be identical in their clinical application and it does not predict their performance in any treatment. Calcium phosphate bone substitute is yet to acquire most desirable mechanical and organic performance and to strike an appropriate growth of curve in volume maintenance of bone graft substitute to achieve ideal success in implant placement.

KEYWORDS

Bone Substitute, Calcium Phosphate, volume Maintenance, Pore Size

INTRODUCTION:

In prosthodontics, the essential thing is to replace the missing tooth. The most recent innovation is dental implants. The bone quantity, morphology and quality are compromised due to severe alveolar bone resorption caused by severe periodontal disease or tooth fracture.^[1,2] Therefore, pre-prosthetic bone graft material / substitute is essential for a successful prosthesis implantation. Objective of bone grafts is to fill the bone in the osseous defect and to stimulate the formation of new bones. The bone graft materials are classified as xenografts, autogenous bone, alloplasts and allografts.^[3] The above-mentioned grafts are, histo-compatable and non-immunogenic and offer the basic properties needed for a bone graft. The present gold standard for bone substitute is the use of autogenous material i.e., bone grafts are harvested from a remote site in the patient body.^[4] Though autografts require a secondary surgery at the donor site, which can prompt difficulties such as contributor site injury, scarring, distortion and morbidity, they possess desirable qualities to achieve osteo-conduction, osteo-induction and osteogenesis. Moreover, autografts may not be a treatment alternative when the defected site requires a lot of bone.^[5] Allografts comprise of freeze -dried human bone with or without demineralization (DFDBA-demineralized freeze- dried bone allograft; FDBA- freeze-dried bone allograft). Xenografts are formed from bovine bone – derived materials that are divided into 2 types according to whether they are subjected to a chemical or thermal deprotenization process (CD-BB- chemically de-protenized bovine bone; TD-BB- thermally de protenized bovine bone). Apart from autografts, benefits have been reported with the use of allografts. These are also restricted in supply and there exists a threat of immune rejection and disease transmission. Corresponding concerns over their utilization prompted the development of various synthetic bone substitutes. One of the most important groups of synthetic bone substitutes are calcium phosphate.^[6] Where calcium phosphates are classified into various types such as octo-calcium phosphate, alpha tricalcium phosphate, beta tricalcium phosphate, amorphous calcium phosphate, hydroxyapatite, fluorapatite, etc.^[7] In which the less frequency used Calcium phosphate are alpha tricalcium phosphate and octo-calcium. The most repeatedly used Calcium phosphate are hydroxyapatite (HA) and beta tricalcium phosphate or an intrinsic combination of the two types of alloplasts have been developed with a view toward control of biological performance based on

physiochemical properties.^[8] An appropriate understanding of these properties, both mechanical and biological are basic for the effective utilization of Calcium phosphate as bone substitutes. None of the currently accessible bone grafts have all the beneficial qualities which a bio-material ought to have such as; angiogenic possibilities, high osteo-inductive properties, biological safety, low patient morbidity, high volumetric strength, simple market accessibility, long time span of usability and sensible production costs.^[9] The present review aims to organize existing knowledge regarding the biological performance/property of volume maintenance in current bone substitute in search of what is optimal for implants in dentistry.

PRE-REQUISITE FOR BONE SUBSTITUTES IN IMPLANT DENTISTRY

PROPERTIES NEEDED FOR BONE FORMATION FROM BONE SUBSTITUTES:

Bone regeneration is commonly done by bone grafting. The unhealthy bones which can't be healed by itself in the human body are repaired and re-build with the use of bone graft.^[10] Bone graft material is placed on a recipient site by a surgical procedure.

This material achieves bone formation because it adheres well to the recipient site.^[11] To perform this sort of repair, we need a structure of porous base which is efficient and bolster a well and new three-dimensional tissue formation is necessary.

- 1) promote, interactivity of cell biomaterial, extra-cellular matrix deposition and adhesion of cells.
- 2) Allow adequate transportation of nutrients, gases and regulative elements to permit propagation survival of cells and differentiation.
- 3) The amount of tissue regeneration is approximated at controllable rate based on biodegradation.
- 4) Incite a minimal level of inflammation.^[12]

The initiation of bone formation on bone substitutes is achieved by osteoprogenitors and mesenchymal stem cells which is acquired from the donor site. The material must aid in the proliferation and differentiation of these cells, which can permit ECM accumulation

formed and harden with the help of osteoblastic cells (oste conductivity). Furthermore, the chance of biological adverse reaction of the material must be reduced (bio-compatibility) and the substance should prevent the collapse of newly created space for bone formation (space-making capability) and ideally be replaced with currently formed bone tissue (regeneration) through bone remodeling and passive chemical dissolution by osteoclasts cells (bio-absorbability).^[13] calcium phosphate substances show a positive interactivity with living tissue which supports to form bone cells from the differentiation process of immature cells.^[14,15]

COMPONENTS FOR THE SPACE MAKING CAPABILITY OF BONE SUBSTITUTES:

Bone remodelling and formation which occurs in the early phases after the new bone formation should be considered separately from the space making capability of bone substitutes. The factors which considerably reduces the volume of new bone formed are the pressure by adjacent tissues such as the gingival or mucosal flap or the schneiders membrane gravity or tissue shrinkage.^[16,17]

ENZYMATIC (OR) CHEMICAL DISSOLUTION:

Tissue forming cells like osteoblast, periosteal cells, macrophages, neutrophils and gingival fibroblast produce different kind of collagenase and it will break down the matrix of collagen.^[18,19,20,21] The compounds of calcium phosphates are used as bone substitute material undergo hydrolysis and they are degraded by tissue fluids.^[22,23] The space making capability are considerably influenced by the sensitivity of chemical or enzymatic dissolution. Prior to the formation of new bone, the bone substitute vanishes, when the passive chemical dissolution reaction is too rapid and leads to defective space formation.^[24]

However, during new bone formation the bone substitute must be retained to support the osteoblast function. More than hydroxyapatite, the water solubility is higher in octo-calcium phosphate and as a result it promotes the new formation of bone to a considerable amount than hydroxyapatite and beta tricalcium phosphate, yet it showed a reducing volume maintenance in the implanted region.^[25,26] Comparatively, the water solubility is excessive in alpha tri calcium phosphate than hydroxyapatite and beta tricalcium.^[27]

MECHANICAL PROPERTIES:

Mechanical properties of graft material will likewise affect the space making capability.^[28] Compressive strength is the important mechanical property of the bone substitutes. More than other bone substitutes, the materials like hydroxyapatite and beta tricalcium phosphate which has non-porous mass form exhibit relatively greater elastic moduli.^[29,30] Since these materials are being used as bone substitutes, we must note that the human cortical bone compressive strength is between 90 and 230 Mpa, while it is between 2 and 45 Mpa for cancellous bone.^[31,32] Calcium phosphates are generally brittle in nature and have little tensile strength which provide limited biomechanical support. Although tricalcium phosphates are less brittle when compared with hydroxyapatite, the outcome shows a rapid loss of mechanical strength over the period of time due to faster degradation of tricalcium phosphate. The result in reduction of mechanical properties is due to increased pore size and porosity.^[33] When the void volume increases it causes reduction of the mechanical strength, which is difficult for the load bearing bones during regeneration process.^[34,35]

PARTICLE SIZE:

Multinucleated giant cells like osteoclasts dissolve smaller (<1mm) particles in bone substitutes ; hence larger amount of the formation of bone is produced from the larger particles of bone substitute.^[36] The volume maintenance from the larger particles of substituted silicate calcium phosphate with the diameter of 250-500 or 1000-2000 μ meter or moderate size is better than the smaller size particles measuring from (90-120 μ meter) ^[37] Within the newly formed bone tissue the larger particles are retained, which owes to the prolonged time need for remodelling or dissolution.^[38,39] For initial bone formation the most important property is space making capability. where the larger particles (>1 mm) create a lump of space with greater mechanical resistance.

FACTORS AFFECTING VOLUME MAINTENANCE AND BIO-ABSORBABILITY OF BONE SUBSTITUTES:

Bio-absorption of bone substitutes has to go through the replacement

process of implanted material. It is done with the help of currently formed bone tissue via bone remodelling that is "regeneration".^[40] Preferably the assessment of new bone formation is similar to the evaluation of resorption of calcium phosphates. The cells responsible for the resorption of calcium phosphates predominantly contains the osteoclasts and multinuclear cells.^[41,42] Generally, compared to calcium phosphates consisting of hydroxyapatite, the calcium phosphates consisting of tri calcium phosphate have higher degradation rates.^[43] In pre prosthodontic surgery, to maintain the alveolar bone three-dimensional morphology and bone volume over the period of time is more important.^[44]

POROSITY AND PORE SIZE:

The basis for the utilization of inorganic bone substitutes is, the presence of interconnected pores.^[45,46] Materials of calcium phosphate contain pores. Where they are important for bone tissue formation and it helps in allowing functions such as proliferation of mesenchymal cells, osteoblast cells as well as vascularization and migration.^[47] The pore size has to be at least 100 μ meter (diameter), where it helps in cell survival from diffusion of nutrients. A pore size from 200-350 μ meter is required for the ingrowth of newly formed bone.^[48] Around the natural bone, pore size gives more prominent mechanical stability at its critical interface. So, Permeable surface improves mechanical interlocking (interdigitation) between the implant biomaterial. Relatively, smaller pores result in osteochondral ossification. Whereas high oxygenation and vascularization are from larger pores which favour direct osteogenesis. The pores geometry and the material used decides the bone ingrowth type within the substitute.^[49,50]

The quality and rate of bone integration is related to the dependence of porosity volume, pore size and interconnectivity.^[51] In addition, bone regeneration requires interstitial fluid and blood, where it helps in transportation of nutrients and oxygen within the local tissue.^[52] Enhanced bone ingrowth, osseointegration after implant surgery are attained from higher porosity and larger pores. The extended surface area outcome gives a greater ion exchange and adsorption of bone. However, the enlarged porosity and pore size may decrease the resistance of mechanical property in few substances and therefore, it has to balance in opposition to the maintenance of volume and the space.^[53]

DISCUSSION:

In general, there is an increasing consciousness of bone substitutes and implants. But we need more qualified and scientific studies to satisfy our dentists that current bone grafts can supply more benefits than existing materials. Bone graft substitutes want to be placed into a strong host position that incorporates enough vascularity and an ample supply of osteoblast precursor cells. In suitable site, these graft substances are ultimately resorbed and replaced with the aid of host bone. Yet, if the operative location is unstable mechanically or if there are insufficient cells or other host substances limiting bone healing, troubles may additionally manifest.

Thus, the clinician has to evaluate the demand of the bone defect to be grafted, contemplate the properties required for repair and eventually select the suitable bone substitute and its related technique for surgery. Graft material that is effective under favourable recipient condition is the autogenous bone graft material. Therefore, "Autogenous bone" is the standard bone graft material and it increase the initiation of bone formation to an eminent extent than other bone substitutes. In the recent times, hybrid substitute for bone graft materials have come into the sight of market.^[54] Which are synthetic materials, which has the lower osteo-inductive property than any of the vital bone graft variety and are not as extensively trusted as the autogenous/allograft materials.

Calcium phosphates are classified into various types such as hydroxyapatite, octo-calcium phosphate, alpha tricalcium phosphate, beta tricalcium phosphate, etc. In which octo-calcium phosphate leads to greater new bone formation compared to hydroxyapatite and beta tricalcium phosphate due to its high-water solubility content. Apart from that, calcium phosphate compounds are degraded by contribution of tissue fluids during hydrolysis process. Therefore, enzymatic / chemical dissolution impacts the space making capability.

Even though every material varies in their compressive strength and mechanical property of bone graft material, it affects the space making capability. Therefore, usually osteoconductive property in tricalcium

phosphate or hydroxyapatite scaffold join together with other elements to magnify the biological or the mechanical performance. Hence, the substitute for bone graft material depends mainly on the clinical application and its co-related mechanical and biological needs.^[55] Apart from this, particle size also influences the property of space making capability. Where the initial bone formation volume is maintained by the larger particles better than smaller particles. Therefore, larger particles increase the space making capability of bone substitutes.

Few factors affect bio-absorption and volume maintenance of bone substitutes. For example, calcium phosphate with hydroxyapatite has comparatively lesser degradation rate than calcium phosphate with tricalcium phosphate. In pre-surgical therapy, it is important to manage the alveolar bone morphology to maintain the volume of bone over a period of time. It is practical to accept that not every substitutes of bone graft will act in the same way and that the validation of a bone substitute at a clinical site may not essentially predict its execution in another location.^[56] For a bone tissue formation, the pore size of calcium phosphate material is very important. The minimum pore size should be at least 100 μ meter for diffusion of materials. The wide assortment of bone substitutes available comprise not just the particular clinical necessities but also it depends on the variety of clinical outcomes. With respect to above statements, we accept that contemporary bone replacement graft materials need to be "resourceful" and bring about a more sensible host response, not only for normal patients but also for more challenging cases.

CONCLUSION:

This review describes the general volume maintenance, space making capabilities and factors affecting the bio-absorption in commercially available bone substitutes.

In precise,

- Autogenous bone graft material is the standard bone substitute which enhance the development of bone formation to a substantial extent rather than other bone substitutes.
- The space making capability is also affected by the particle size, chemical or enzymatic dissolution and mechanical properties.
- The volume maintenance and bio-absorption of bone substitutes is affected by the element of porosity and pore size.
- These days the accessible bone substitutes bring about only osteo-conductivity as a stage and no osteo-inductivity.
- Currently, no absolute bone substitute exists. At the same time, they won't reveal the satisfactory volume maintenance, space making capability and bio absorption.
- Therefore, the volume maintenance of present substitute of bone materials has to be enhanced.

REFERENCES:

- Axelsson P, Nyström B, Lindhe J. The long term effect of a plaque control program on tooth mortality, caries and periodontal disease in adults. Results after 30 years of maintenance. *J clin periodontol* 2004; 31:749-57.
- Egusa H, Sonoyama W, Nishimura M, Atsuta I, Akiyama K. Stem cells in dentistry – part 1: stem cell sources. *J Prosthodont Res* 2012; 56:151-65.
- Mish CE, Dietsch F. Bone-grafting materials in implant dentistry. *Implant dent* 1993; 2:158-67.
- Giannoudis, Chris arts, Schmidmaier and Larsson, 2011, De Grado et al, 2018
- Ebraheim, Elgafy and Xu, 2001, St John et al, 2003
- Legeros RZ. Properties of osteoconductive biomaterials: calcium phosphates. *Clin orthop relat res* 2002;81-98
- Sudip mondal, Sergiy v. Dorozhkin, Umapada pal. Recent progress on fabrication and drug applications of nanostructured hydroxyapatite.
- Legeros RZ, Lin S, Rohanizadeh R, Mijares D, Le geros JP. Biophasic calcium phosphate bioceramics: preparation, properties and application. *J mater med* 2003;14: 201-9
- Bose, Roy and Bandyopadhyay, 2012, Hutmacher, 2006, El-Rashidy, Harhaus, Kneser and Bocaccini, 2017.
- Huiskes, Ruimerman, Van lenthe and Janssen, 2000
- Bone augmentation and nerve repositioning, Available from <https://www.colgate.com/en-us/oral-health/cosmetic-dentistry/implants/bone-augmentation-and-nerve-repositioning>.
- Langer R, Tirrell DA. Designing materials for biology and medicine. *Nature* 2004; 428:487-92.
- Karageorgiou and Kaplan, 2005; Murphy, Haugh and Obrion, 2010; Saito et al, 2012
- L.L. Hench, " Bioceramics: from concept to clinic", *Journal of the American ceramic society*, vol.74, pp.1487-1510,1991.
- T.V. Thamaraiselvi and S. Rajeshwari, "Biological evaluation of bioceramic materials: a review", *Trends in biomaterials and artificial organs*, vol.18, no.1, pp.9-17,2004.
- Tejero- Trujequé R. Understanding the final stages of wound contraction. *J wound care* 2001;10:259-64.
- Harris GJ, Perez N. Anchored flaps in post- moles reconstruction of the lower eyelid, cheek and lateral canthus: avoiding eyelid distortion- ophthal plast reconstruction surgery 2003;19:5-13.
- Romanelli R, Mancini S, Laschinger C, Overall CM, Sodek J, McCulloch CA. Activation of neutrophil collagenase in periodontics. *Infect immune* 1999;67:2319-26.
- Wahl LM, Olsen CE, Sandberg AL, Mergenhagen SE. Prostaglandin regulation of macrophage collagenase production. *Proc natl acad sci USA* 1977;74:4955-8
- Bord S, Horner A, Hembry RM, Reynolds JJ, Compston JE. Production of collagenase by human osteoblasts and osteoclasts in vivo. *Bone* 1990;19: 35-40.
- Wilhelm SM, Javed T, Miller RL. Human gingival fibroblast collagenase: purification and properties of precursor and active forms. *Coll relat res* 1984;4: 129-52.
- Monteiro MM, Da Rocha NCC, Rossi AM, Soares GDA. Dissolution properties of calcium phosphate granules with different compositions in simulated body fluid. *J Biomed mater res A* 2003;65: 299-305.
- Dorozhkin SV. Calcium orthophosphates in nature, biology and medicine. *Materials* 2009;2: 399-498.
- Koide M, Osaki K, Konishi J, Oyama K, Katakura T, Takahashi A, et al. A new type of biomaterial for artificial skin: dehydrothermally cross-linked composites of fibrillar and denatured collagens. *J Biomed mater res* 1993;27: 79-87.
- Suzuki O, Kamakura S, Katagiri T. Surface chemistry and biological responses to synthetic octacalcium phosphate. *J Biomed mater res B Appl biomaterial* 2006;77: 201-12.
- Kamakura S, Sasano Y, Shimizu T, Hatori K, Suzuki D, Kagayama M, et al. Implanted octacalcium phosphate is more resorbable than beta-tri calcium phosphate and hydroxyapatite. *J Biomed mater res* 2002;59: 29-34.
- Carrodegus RG, De aza S. Alpha – tricalcium phosphate: synthesis, properties and biomedical applications. *Acta biomater* 2011;7: 3536-46.
- Tovar N, Jimbo R, Marin C, Witek L, Suzuki M, Bonfante EA, et al. Bone regeneration around implants placed in fresh extraction sockets covered with a dual-layer PTFE/collagen membrane: an experimental study in dogs. *Int J. Periodontics restorative dent* 2014;34:849-55.
- Amaral M, Lopes MA, Silva RF, Santos JD. Densification route and mechanical properties of Si3N4-bioglass biocomposites. *Biomaterials* 2002;23: 857-62.
- Liang L, Rulis P, Ching WY. Mechanical properties, electronic structure and bonding of alpha and beta- tricalcium phosphates with surface characterization. *Acta biomater* 2010;6: 3763-71.
- An YH. Mechanical properties of bone. In: An YH, Draughn RA, editors. *Mechanical testing of bone and the bone-implant interface*. Boca Raton: CRC Press;2000 P.41-64.
- Ginebra MP. Calcium phosphate bone cements. In: Deb S, editor. *Orthopaedic bone cements*. 1st ed. Cambridge, England: Woodhead publishing limited; 2008. p.206-30.
- Karageorgiou V, Kaplan D. Porosity of 3D biomaterial scaffolds and osteogenesis. *Biomaterials* 2005;26: 5474-91.
- Blokhuis TJ, Termaat MF, Den Boer FC, Patka P, Bakker FC, Haarmann HJ. Properties of calcium phosphates ceramics in relation to their in vivo behaviour. *J. Trauma* 2000;48: 179-86.
- Lane JM, Bostrom MP. Bone grafting and new composite biosynthetic graft materials. *Instruments course lecture* 1998;47: 525-34.
- Chackartchi T, Lezzi G, Goldstein M, Klinger A, Soskolne A, Piattelli A, et al. sinus floor augmentation using large (1-2mm) or small (0.25-1 mm) bovine bone mineral particles a prospective, intra- individual controlled clinical, micro- computerized tomography and histomorphometric study. *Clin oral implants res* 2011;22473-80.
- Coathup MJ, Cai Q; Campion C, Buckland T, Blunn GW. The effect of particle size on the osteointegration of injectable silicate- substituted calcium phosphate bone substitute materials. *J. Biomed mater Res B Appl biomater* 2013;101: 902-10.
- Prieto EM, Talley AD, Gould NR, Zienkiewicz KJ, Drapeau SJ, Kalpakei KN, et al. effects of particle size and porosity on in vivo remodelling of settable allograft bone/polymer composites *J Biomed mater Res B Appl biomater* 2015;103:1641-51.
- Pallensen L, Schou S, Aaboe M, Hjorting- hansen E, Nattestad A, Melsen F. influence of particle size of autogenous bone grafts on the early stages of bone regeneration: a histologic and stereologic study in rabbit calvarium. *Int J oral maxillofacial implants* 2002;17: 498-506.
- Egusa H, Sonoyama W, Nishimura M, Atsuta I, Akiyama K. Stem cells in dentistry- part 11: clinical applications. *J. Prosthodont Res* 2012;56:229-48.
- Yamada S, Heyman D, Boulter JM, Daculsi G. Osteoclastic resorption of calcium phosphate ceramic in vitro. *J. Biomed mater res* 1997;37: 346-52.
- Yamada S, Heyman D, Boulter JM, Daculsi G. Osteoclastic resorption of calcium phosphate ceramics with different hydroxyapatite/ beta-tricalcium phosphate ratios. *Biomaterials* 1997;18: 1037-41.
- Hing KA. Bone repair in the twenty first century: biology, chemistry or engineering? *Philos trans A math phys eng sci* 2004;362: 2821-50.
- Funato A, Ishikawa T, Kitajima H, Yamada M, Moroi H. A novel combined surgical approach to vertical alveolar ridge augmentation with titanium mesh, resorbable membrane, and rhPDGF-BB: a retrospective consecutive case series. *Int j periodontics restorative dent* 2013;33: 437-45.
- Rouwkemka J, Rivron NC, Van blitterswijk CA. vascularization in tissue engineering. *Trends biotechnol* 2008;26: 434-41.
- Skedros JG, Clark GC, Sorenson SM, Taylor KW, Qius. Analysis of the effect of osteon diameter on the potential relationship of osteocyte lacuna density and osteon wall thickness. *Anat rec (Hoboken)* 2011;294: 1472-85.
- Gerjon Hannink, J.J. Chris arts. Bioresorbability, porosity and mech. Strength of bone substitutes: what is optimal for bone regeneration? *Injury, int. j. care injured* 42(2011) s22-s25.
- Murphy CM, Haugh MG, O'Brien FJ. The effect of mean pore size on cell attachment, proliferation and migration in collagen- glycosaminoglycan scaffolds for bone tissue engineering. *Biomaterials* 2010;31: 461-6.
- Hockers T, Abensur D, Valentini P, Legrand R, Hammerle CH. The combined use of bioresorbable membranes and xenografts or autografts in the treatment of bone defects around implants. A study in beagle dogs. *Clin oral implants res* 1999;10:487-98.
- Atari M, Chatakun P, Ortiz O, Manes A, Gil-Recio C, Navarro MF, et al. viability of maxillary bone harvesting by using different osteotomy techniques. A pilot study. *Histology histopathology* 2011;26: 1575-83.
- Hing KA. Bioceramic bone graft substitutes: influence of porosity and chemistry. *Int J appl ceramic technology* 2005;2: 184-99.
- Tomlinson RE, Silva MJ. Skeletal blood flow in bone repair and maintenance bone res 2013;1: 311-22.
- Masahiro Yamada, Hiroshi Egusa/ *Journal of prosthodontic research* 62(2018)152-161.
- Low KL, Tan SH, Zein SH, Roether JA, Mourino V, Bocaccini AR. Calcium phosphate based composites as injectable bone substitute materials. *J. Biomed mater res B appl biomater* 2010;94: 273-86.
- Beaman FD, Bancroft LW, Peterson JJ, Kransdorf MJ. Bone graft materials and synthetic substitutes, radiol clin north am 2006;44:451-61.
- Giannoudis PV, Einhorn TA, Marsh D. Fracture healing: the diamond concept. *Injury* 2007;38(suppl4): s3-6.