IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 13, Issue 9 Ver. III (Sep. 2014), PP 83-91
www.iosrjournals.org

Porous Titanium Granules

Dr. Meera Avadnani,[1] Dr. K. Mahalinga Bhat,[2] Dr. Meena Anand[3]
[1.] *Postgraduate student, Department of Periodontology. Manipal College of Dental Sciences, Manipal.*
[2.] *Professor. Department of Periodontology. Manipal College of Dental Sciences, Manipal.*
[3.] *Associate Professor. Department of Periodontology. Manipal College of Dental Sciences, Manipal.*

Abstract: *Bone grafts are invaluable players in the arena of regenerative dentistry. Reconstitution of the lost bone was the objective behind the introduction of these bone grafts based on the properties of osteoconduction, osteoinduction and osteogenesis. Although autogenous bone grafts still uphold their reputation as gold standard, certain issues like the unpredictable quantity and the donor site morbidity limited its usage. Allografts too have their own shortcomings. Subsequently, significant efforts are in progress in the development of ideal bone graft substitutes.*
A range of alloplasts starting from hydroxyapatite and tricalcium phosphate to the currently available nanoparticles, titanium granules are available in the market. Some of these are resorbable while others are not. The point of issue at this juncture is how far are these materials effective in promoting regeneration. In the course of finding a solution, researchers ended up with varied sources for procuring suitable bone grafts.
One such resource is Titanium and its availability in the form of porous granules popularly known as porous titanium granules represents a new possibility in augmenting osseous regeneration.
The aim of the present review paper is to discuss the characteristics, added benefits as well as different applications of this material with a varied range of success in the field of clinical practice.
Key Words: *PTGs, bone graft, osteoconduction, regeneration, thrombogenicity*

I. Introduction

Bone grafts are an invaluable contribution to the field of regenerative dentistry. Reconstitution of the lost bone was the objective behind the introduction of these bone grafts based on the properties of osteoconduction, osteoinduction and osteogenesis. Bone grafts are necessary to provide support, fill voids, and enhance biologic repair of skeletal defects.The first use of bone grafts in the periodontal therapy is credited to Hegedus[1]. Histologic evidence in humans indicates that bone grafting is the only treatment that leads to regeneration of bone, cementum, and functionally oriented new periodontal ligament coronal to the base of previous osseous defect. Based on the sources of procurement, these bone grafts are classified as autologous (bone harvested from the patient's own body), allograft (cadaveric bone usually obtained from a bone bank), Xenograft (grafts procured from other species) or synthetic (often made of hydroxyapatite or other naturally occurring and biocompatible substances) with similar mechanical properties to bone. Most bone grafts are expected to be reabsorbed and replaced by bone over a period of few months.

II. The Rationale behind bone grafting

Bone grafting is possible because bone tissue, unlike most other tissues, has the ability to regenerate completely if provided the space into which to grow. As native bone grows, it will generally replace the graft material completely, resulting in a fully integrated region of new bone. The biologic phenomena that provide a rationale for bone grafting are osteoconduction, osteoinduction and osteogenesis.[2]

Osteoconduction

Osteoconduction occurs when the bone graft material serves as a scaffold for new bone growth that is perpetuated by the native bone. Osteoblasts from the margin of the defect that is being grafted utilize the bone graft material as a framework upon which to spread and generate new bone.[1]In the very least, a bone graft material should be osteoconductive.

Osteoinduction

Osteoinduction involves the stimulation of osteoprogenitor cells to differentiate into osteoblasts that then begin new bone formation. The most widely studied type of osteoinductive cell mediators are bone morphogenetic proteins (BMPs).[2]A bone graft material that is osteoinductive will not only serve as a scaffold for currently existing osteoblasts but will also trigger the formation of new osteoblasts, theoretically promoting faster integration of the graft.

Osteopromotion

Osteopromotion involves the enhancement of osteoinduction without the possession of osteoinductive properties. For example, enamel matrix derivative has been shown to enhance the osteoinductive effect of demineralized freeze dried bone allograft (DFDBA), but will not stimulate de novo bone growth alone[3].Most of the growth factors currently being used fall in to this category.

Osteogenesis

Osteogenesis occurs when vital osteoblasts originating from the bone graft material contribute to new bone growth along with bone growth generated via the other two mechanisms[2].

Properties of various types of bone graft sources[2].

	Osteoconductive	Osteoinductive	Osteogenic
Alloplast	+	–	–
Xenograft	+	–	-
Allograft	+	+/–	-
Autograft	+	+	+

Although the above table illustrates the reputation of the Autogenous bone grafts as the gold standard, certain issues like the unpredictable quantity and the chronic donor site morbidity limited its usage.

There was an increase in the search for alternative bone grafts. Allografts may be cancellous, cortical, or a combination of each. Though they are attractive sources, there are several problems encountered in using them, including the risk of disease transmission, immunogenicity,[3] loss of biologic and mechanical properties secondary to its processing, increased cost, and non-availability world-wide due to financial and religious concerns. Patient reservations in readily accepting allografts is another constraint. Subsequently, significant efforts are in progress in the development of ideal bone graft substitutes.

A plethora of alloplasts have been tried starting from the age old Plaster Of Paris, hydroxyapatite and tricalcium phosphate to the currently available nanoparticles, titanium granules etc. Some of them claim to be resorbable while others are not. The point of issue at this juncture is how far are these materials effective in promoting regeneration. In the course of finding an answer, researchers ended up using varied sources for procuring suitable bone grafts. This review deals with one such source i.e Titanium and its availability in the form of porous granules popularly known as porous titanium granules.

Titanium - A body friendly metal

Titanium alloys[4] are considered to be the most attractive metallic materials for biomedical applications and Ti-6Al-4V had long been favored for the same. However, for permanent implant applications the alloy had a possible toxic effect resulting from released vanadium and aluminum. For this reason, vanadium- and aluminum free compositions have been introduced for implant applications.

Commercially pure titanium (Cp Ti) is considered to be the best biocompatible metallic material because its surface properties result in the spontaneous build-up of a stable and inert oxide layer.

The main physical properties of titanium responsible for the biocompatibility are

1. Low level of electronic conductivity,
2. High corrosion resistance,
3. Thermodynamic state at physiological pH values,
4. Low ion-formation tendency in aqueous environments, and
5. A suitable iso-electric point of the oxide.
6. The elastic modulus of Ti is similar to that of bone.

In addition, the passive-film-covered surface is only slightly negatively charged at physiological pH, and titanium has a dielectric constant comparable to that of water with the consequence that the Coulomb interaction of charged species is similar to that in water.

The most fascinating features of titanium include the ability of its particles to stimulate complement and platelets[5].Also, the material was proficient in activating the coagulation system with thrombus formation as a result of blood contact. Stimulation of the coagulation and the complement systems initiates the adsorption of plasma proteins on to the surface. This process is followed by the activation and adhesion of platelets and leukocytes[5]. Thus, the clot establishment and wound stabilization are in a way accelerated with its use. The platelets consequently increase the level of platelet-derived growth factor which has been shown to promote bone growth[6]. All these features add up to Titanium's bio-inert nature.

The use of titanium as well as tantalum and indium in an in vitro study were found to display pronounced platelet attracting properties. Aluminium, nickel, and especially iridium were regarded as non-thrombogenic[7].

Porosity and its significance:

Considering the special features of Ti, researchers observed that surface modifications of this element brought about miniature changes in its osseointegration. From then onwards many modifications have been introduced like blasting with TiO2, etching with Hydro Fluoric acid (HF), other chemical modifications as well as nanotubes of TiO2. This nano architecture when experimented resulted in better proliferation and adhesion of osteoblasts resulting in improved bone bonding strength as compared to TiO2-gritblasted surfaces[8].
This observation drove a direct relationship between the extent of thrombogenecity and the size of the nanopores. An additional finding was that the platelet activation was higher in the pore size of about 200nm.
It was the incorporation of these nanoporous architecture to titanium which brought Porous Titanium Granules (PTG's) in to lime light.

Furthermore, the porous titanium granules are hollow in their total volume to 80 percent which facilitated the capillary action[7] on blood to fill these pores which parallelled the initiation of coagulation cascade and release of growth factors.This event clinically resulted in the formation of a moldable mass that can be easily placed in to the defects.

Porous Titanium Granules

Porous Titanium Granules represent a new possibility in augmenting osseous defects in the field of regeneration. They are commercially available under the trade names of "Tigran", "Natix", "Ortrix" etc. A typical porous titanium granule is 500–1,000 nm in diameter but the total titanium surface of the ultra-porous granules is close to 2 cm^2 according to the analyses performed by the manufacturer[9].

Characteristics of PTG :

Tigran™ PTG (Porous Titanium Granules) is made of body-friendly titanium, known for more than 40 years as a superior material for dental implants. This novel bone regeneration material combines the superior biocompatibility, mechanical strength and osteoconductivity of titanium with an ultra-porous architecture that acts as an excellent scaffold for the growth of new bone. Tigran™ PTG has many applications for medical and dental bone regeneration, the most common are sinus lift, regeneration of bone in peri-implantitis defects and post-extraction socket fillings.

Tigran supplies 2 forms of Porous titanium granules, the regular metallic PTG as well as the oxidized form i.e White PTG (WPTG). It was observed that PTG is 80% porous whereas WPTG is only 56% porous[9]. Both are superior in their own ways.

Differences between PTG and WPTG

PTG	WPTG
Regular metallic color	Oxidized form – white in color
80% porous	56% porous
Black hue on the outer surface of the tissues	Doesn't blacken – anterior esthetic zones

It is composed of 80% air and 20% pure titanium acting as a unique scaffold for bone in-growth and provides for optimal osseointegration. Also a normal osteotomy procedure can be used since a soft titanium grade 1 was used. It is non-resorbable leading to permanent volume fill and predictable long-term results with optimal function and esthetics.

It is irregular in shape with interconnected pores and platelet attracting properties. It acquires immediate mechanical stability through the combined role of porosity and capillary action, quickly forms a blood clot and hence easy to handle.

Advantages of Porous Titanium granules

Porous titanium granules are known to offer several advantages[10]when compared with other bone graft materials:

1. Most importantly, the titanium granules are not resorbed, which means that the joint surface congruity achieved during surgery is maintained during the healing period.
2. Further advantages include its easy accessibility and eliminated risk of contagion.
3. The titanium granules do not set (i.e. no risk of heat injury to the bone) and can therefore be handled without time pressure during surgery.
4. Moreover, the fact that no bone needs to be harvested from the donor site means shorter surgery time and less pain for the patient.

The literature reports that it was L. Holmberg in 1995, who first used these Porous titanium ganules along with autogenous blood for the augmentation of the dento-alveolar ridge in a severely resorbed maxilla in a 73yr old patient[11]. He used these granules as fillers following a split crest technique and followed up for around 12 long years. The clinical and radiographic results were excellent and well maintained even after 12 yrs.

It was L.Holmberg's piece of observation which paved a way for the wide usage of this material in the field of Orthopaedics with great predictability.

PTG in Orthopedics:

Alffram P-A et al[12] successfully used titanium granules for the implantation of the femoral stem in 5 patients more than 15yrs ago. It was an encouraging clinical finding. Researchers even appreciated the histological changes in the tissues when these granules are used. Thomas M. Turner et al in 2007[13] used porous titanium granules for cement-less fixation of a hip replacement femoral stem in an established canine hemi-arthroplasty model in dogs and followed up for 6 months. The dogs continued to exhibit normal clinical usage of the limb throughout the six-month study period and without any radiological signs of loosening. Their histological observation revealed lamellar bone formation through the bed of granules in continuity with the surrounding cortex as well as a direct contact between the bone and the prosthesis in few areas.
They also reported a firm initial stabilization of the prosthesis using these granules.
They extended their trials on to humans considering earlier observations in animals.

Brynjolfurjonsson et al (2009)[14] used porous titanium granules in the surgical treatment of depression fractures of the lateral tibial plateau in 4 patients. They observed excellent clinical stability and radiographical results.
An issue was raised regarding the small size of the Ti particles that they obliterated the bone chamber when tightly compacted affecting its osteoconductivity.

Lucas H Walschot et al (2011)[15] observed the effect of impaction and a thin silicated biphasic calcium phosphate coating on osteoconduction by Ti particles in goats. They used impacted allograft bone particles as controls. Ti particles showed good fibrous armoring, but inferior osteoconduction compared to allograft bone, especially after impaction. In this study, the small Ti particles tended to obliterate the lumen of the bone chamber.

This particular finding gave a clue regarding the extent of compaction required for these granules to achieve better outcomes.

PTG in Dentistry

Following L.Holmberg's observation, PTG's have gained popularity in the field of Oral and Maxillofacial surgery as a bone graft substitute for the augmentation of sinus floor.
The non-resorbable property of PTG favored its wide usage in cases like ridge augmentation, sinus floor elevation etc.

Sinus Floor Elevation:

Bystedt H et al (2009)[16] performed a clinical pilot study where they tested titanium granules as bone substitute in patients planned for augmentation of the sinus floor prior to or in conjunction with placement of dental implants. The follow up was done for 12 to 36 months after prosthetic loading. They reported on the outcome after having treated 16 patients with a total of 23 implants. The implant survival rate, evaluated between 12 and 36 months after functional loading of the implants, was 87%. Although they were able to successfully augment the sinus floor, their minor observations like mobility in case of 3 implants cast a doubt regarding the safety of this material in a 2 stage procedure.

Their findings brought in to light certain queries like the length of healing time required after augmenting and before implant installing, the possible risk of granule displacement during the preparation of the fixture site and also whether there is any bone ingrowth occurring between the granules.

However, the work carried out by Lambert F et al and others attempted to figure out the raised queries.
Lambert F et al (2013)[17] evaluated the use of PTG for sinus lift in rabbits qualitatively and quantitatively. They performed double sinus lift procedure and used 3 different materials namely : grade I porous titanium granules, Bovine hydroxyapatite (BHA) as well as Bovine Hydroxyapatite hydrated with doxycycline solution (0.1mg/ml) (BHATTC). At 6 months, the 3-D volume stability was higher in Ti group and BHATTC group. However, the bone to material contact indicating osteoconduction was relatively lower in Ti group. The study team

confounded that all the 3 materials were relevant candidates for sinus floor augmentation prior to implants as they showed acceptable 3-D stability and osteogenesis.

However, to recommend the clinical use of Ti, both an observation on the effect of osteotomy of the site preparation on Ti particles and clinical trials are needed.

Vandeweghe S (2013)[18] compared and evaluated PTG with the well known osteoconductive material i.e Deproteinized bovine bone particulates (Bio-Oss) in humans. They executed sinus grafting procedure using these 2 materials in contralateral sites in 2 patients. After 9 months, biopsies were performed and evaluated histologically. It was observed that both the materials were in contact with newly formed bone but those grafted with Bio-Oss elicited foreign body reaction. Surprisingly, bone filled the space between the single porous titanium granule and did not elicit any such adverse reaction. So, from the bone formation and biocompatibility perspective, PTG's can be considered as an alternative treatment option for sinus grafting.

Confirming Vandeweghe's observation, **Verket et al (2013)**[19] also observed bone ingrowth in to PTG's when used for sinus augmentation. 6 months after placing graft in to the sinus, they noted that the new bone formed has a similar rate and quality as that of other bone graft substitutes.

Though further research is awaited in this area, the available evidence emphasizes the use of PTG's for sinus lift procedures.

Peri-implant defects

Dentists are truly allured in finding new treatment modalities for treating peri-implantits and to regenerate the bone that was lost due to infection. The wide range of treatment options include conservative , resective and regenerative procedure in conjunction with various modes of surface decontamination. In view of bone grafts when used for regeneration of the defects, **Claffeyet al**[20] specified that these materials most of the times do not result in disease resolution but merely put an effort to fill the osseous defect[20]. Consequently new regenerative materials are welcomed by the clinicians and PTG is nevertheless one such strategy.

It was **Johan Caspar Wohlfahrt et al (2010)**[9] investigated the osteoconductive properties of porous titanium granules using a peri-implant defect model in the tibial bone of 24Newzealand rabbits. They used both metallic and oxidized porous titanium granules(PTG/WPTG) for treating the test defects followed by implant placement. The defects were left for healing for 4 weeks and after healing, the implants were removed. They observed more amount of new bone formation in the PTG/WPTG treated sites than controls. They also noted that the mineralized tissue is forming directly on to the granules as well as filling the space between the granules. This finding once again highlighted the osteoconductive property of the granules.

The WPTG group showed significantly less expression of key inflammatory markers, but with no significant difference in a marker for necrosis i.e LDH(Lactate Dehydrogenase). The WPTG also showed significant increase in collagen-I mRNA expression compared with PTG indicating a higher bone matrix deposition in the defects treated with WPTG.

They also attempted to reason out the mechanism of bone formation with the help of these granules followed by placement of implants into the bone marrow.

The bone marrow is an interesting tissue from the perspective of osseous regeneration. Not only does the bone marrow contain mesenchymal progenitor cells that can differentiate to osteoblasts, but it is also rich in vasculature, providing a supply of circulating mononuclear precursors that differentiate into osteoclasts and endothelial cells needed for neo-angiogenesis **(Davies 2003)**[21]. The tibial bone in rabbits does not exhibit trabecular bone structures in the bone marrow space. The histological observation of trabecular bone growth where granules were applied consequently suggests that the titanium granules also act as an osteoconductive scaffold when placed in the bone marrow. This bone may originate from the cortex, growing along the surfaces of the titanium granules into the subjacent marrow compartment. This assumption is supported by the observation that new trabecular bone always included titanium granules.

Another possible mechanism involved in bone formation in the marrow space compartment may be by bone apposition directly onto the implant surface also called contact osteogenesis **(Osborn & Newesley 1980)**[22].

Taking in to consideration the LDH levels, the safety aspects of this material were re-assured.

It was noted by **Wilke et al (2002)**[23] in an in vitro experiment that exposure to particles consisting of titanium–vanadium–aluminum can stimulate an increased release of LDH, which is a reliable marker for tissue necrosis.

Torgersen et al (1995)[24] made an observation that when small metal particles(<1μm) were implanted in to the tissues, sometimes they were found within the cytoplasm of macrophages. Encapsulation by connective tissue with minimal inflammatory response was noted when larger particles(>1μm) were implanted. However both the PTG as well as WPTG comprise of titanium granules 500-1000μm in diameter.

In their study **Wohlfahrt et al** also made an observation on the levels of inflammatory biomarkers. They observed significantly lower levels of TNF-α in defects treated with WPTG than others. The total amount of protein in the wound fluid was also less in WPTG group when compared to PTG and control groups.

These findings emphasized the anti-inflammatory response of the TiO_2.

Viewing at the minor differences in the responses with both the titanium granules, it raises a suspicion that the degree of oxidization might have an impact on the anti-inflammatory mechanisms of these granules. However, Wohlfahrt says that it is too early to draw conclusions as they did not observe significant changes in other inflammatory markers like IL-6, IL-10 etc.

Nonetheless, their study was able to answer many queries regarding the regenerative role played by these granules and paved way for further human trials.

Wohlfahrt (2011)[25] used these granules for the treatment of a case of peri-implant osseous defect and analysed it histologically. Following open flap debridement of the defect, root conditioning and grafting with PTG was done. Histological analysis after 12 months of healing gave a picture of PTG lying in close contact with new bone and with bone growing both in to the porosities of the granules and on to the adjacent implant surface. Elemental analysis also demonstrated calcium and phosphorus in the new tissue embedding the PTG and the implant.

Plastic instruments are widely used for the debridement of implant surfaces. However, **Mann et al**[26] demonstrated that instrumentation with plastic-covered ultrasonic inserts lead to remnants of plastic on the implant surface. So, **Wohlfahrt (2011)** came up with a new idea of using a novel titanium brush oscillating at 800rpm in a dental hand piece for debriding implant surfaces.

Wohlfahrt[24] debrided a narrow peri-implant osseous defect with a titanium brush[27] oscillating at 800rpm for around 2 min following which he irrigated with 3% H2O2 and saline. After this, PTG were optimally compacted in to the defect. After 6 months of healing, the PTG appeared completely integrated, with no signs of dislodged PTG particles. New bone was also present coronal of the PTG particles and covering the buccal section of implant.

This case brought in to light a new potential treatment modality for the treatment of narrow peri-implant osseous defects with a titanium brush followed by grafting with PTG's.

E. Mijiritsky et al (2013)[28] evaluated the preliminary use of PTG for the treatment of peri-implantitis lesions in humans. They performed a retrospective observation on 16 patients with 18 peri-implantitis defects, treated with OFD and grafted with PTG and followed them for about 6-15 months. Mean bone loss prior to treatment was 4.4 ± 2.1 mm and was reduced following treatment to 2.3 ± 2.1 mm. They presented with a clinical success rate of 88% with 2 implants still bled on probing with suppuration. Though their observations seems to be acceptable, the results cannot be generalized due to varied reasons like the type of observation (retrospective) and sample size etc.

Recently in 2013, **Andreas Thor**[29] came up with an excellent report on the use of PTG's in 4 cases of defects around dental implants. Following debridement of the defect using titanium brush (Tigran brush no.1) , rinsing was performed with 3% H2O2 followed by saline irrigation. Later small bur was used in the walls of the defect to induce fresh bleeding and mixed these granules with blood. The granules got well connected within the clot and formed in to a lightly moldable mass ready for augmentation. They observed a clinically and radiographically stabilized situation with no bleeding and exudation and also halted bone loss even after a follow up of 9 - 26 months.

They explained that blood acts as a primary tissue in "gap"bony healing and stressed on the thrombogenic and platelet - activating property of Titanium for the regenerative response.

It seems logical to use these granules for the surgical management of peri-implant defects because of their similar compositions.

Socket preservation

It was PTG's novel features like non-resorbability, space maintaining ability , high osteoconductivity and an elastic modulus similar to alveolar bone attracted many researches to evaluate PTG's for augmenting extraction socket and preserving alveolar ridge morphology.

Bashara H and Wohlfahrt (2012)[27] evaluated the effect of these granules in case of socket preservation in 6 beagle dogs with and without the use of a barrier membrane. They also compared the effect of these granules with a deproteinized bovine bone xenograft (DBBX).

Their results were not successful in proving any technique superior to other. Nonetheless, they observed better bone maturation when used in combination with a barrier membrane after 6 months of healing. Also, their findings once again complemented the osteoconductive nature of these granules.

Around the same time**, Tavakoli et al**[30] also performed a similar study using Tigran alone with a barrier membrane in dogs. They observed that after 2 weeks of healing that the amount of regenerated woven bone was maximum in control group(with out PTG's and barrier membrane) while it was minimum in the Tigran + membrane group.

Then again at 6 weeks, the amount of regenerated lamellar bone reached its peak in the Tigran+membrane group. It was also observed the difference between the membrane alone and Tigran+membrane group was not statistically significant. This particular piece of information again stresses on the osteopromotive property of the membranes which inhibit the epithelial cell proliferation and down migration in to the defect as well as give an opportunity to bone cells to play their role. The study revealed out a novel usage of PTG with barrier membranes for better outcomes.

Recently, a similar observation was also made by **Delgado-Ruiz R A et al**[31] in the tibia of rabbits through critical size defects. They observed more defect closures and more amount of new bone formation in the defects treated with PTG followed by barrier membrane rather than PTG's alone. Finally, inflammatory reactions were noted when the granules were not protected by membranes.

These findings inferred that PTG's must be covered by barrier membranes especially when grafting larger defects, in order to control particle migration, promote clot stabilization and separate the graft from undesired soft tissue cells.

Following extraction socket preservation with these granules, Wohlfahrt along with his co-workers also tried placing implants in to these sites.

Verket A and Wohlfahrt et al (2012) [32] investigated osseointegration of dental implants inserted in healed extraction sockets preserved with porous titanium granules (PTG) in 3 minipigs. The sockets were preserved using PTG, WPTG and some were left alone. All the sockets were covered by a barrier membrane. After a period of 11 weeks of healing, implants were inserted in to these sockets. After 6 weeks of post-implant healing period, the pigs were sacrificed and analysed. The average bone volume was relatively more for PTG group when compared to WPTG as well as sham group. However, it was not statistically significant. The bone to implant contact was also high in PTG group when compared to WPTG group. Implants in all groups developed apical lesions. However, they were relatively more in the WPTG group. The causing circumstances for such lesions are largely unknown. Previously reported speculations include overcompression of bone during implant placement leading to localized pressure necrosis of bone, latent infection activated by surgical trauma, systemic disease which has affected local healing, and implant contamination during surgery (**Bashutski et al. 2009**)[33]. This area needs to be addressed further in detail with more extensive research.
These studies stressed on the use of PTG for preserving extraction sockets.

Periodontal defects:

Wohlfahrt, after using these granules for treating peri-implantitis defects, further extended his trials on to its usage in periodontal defects.

Wohlfahrt (2012) [34] compared the potential of PTG's with Deproteinized Bovine Bone Mineral (DBBM) in the treatment of surgically created grade II buccal furcation defects in mini pigs.

After 6 weeks of healing, the histological analysis revealed significantly more bone formation in PTG compared to DBBM treated defects. The results of this study in mini-pigs suggested that PTG may integrate well in alveolar bone and support osseous regrowth in grade II furcation defects. Also, approved the safety of use of PTG close to root surfaces.

After being assured of the findings in minipigs, Wohlfahrt (2012)[35] evaluated a surgical treatment strategy based on the use of PTG in the treatment of Class II buccal furcation defects in mandibular molars in humans and came up with a series of cases. No significant changes were observed in relation to horizontal and vertical bone sounding measurements, gingival recession as well as Clinical attachment level even at the end of 12 weeks. However, the probing pocket depth and radiographic vertical furcation height were significantly reduced between baseline and 12 months. The gingival index score was also reduced albeit, no change in bleeding on probing re-emphasizing Claffey's[20] statement that the use of the bone grafts most of the times result in defect fill rather than true disease resolution.

III. Biocompatibility of PTG's:

Around the same time when PTG's were gaining popularity in the field, **Gholami in 2010**[36] in an animal study (in the tibia of dogs) compared the quality and quantity of new bone formed when 3 different bone grafting materials were used namely : Bio-Oss, Bio-Gen and PTG with and without barrier membranes. He

observed that after 3 months of healing, the amount of new bone formation in PTG's was similar to that of Bio-Oss + collagen membrane and also that the quality of the bone formed was much better in the PTG group. He noted that application of PTG's did not interfere with the initial healing of the wound. He found that the bone marrow around PTG was fatty & vascular unlike in other groups indicating that the bone remodelling process was progressing normally. The density of the bone trabeculae and the penetration of the bone between the granules indicate that PTG helps in the formation of cortical bone. These findings are in favor of biocompatibility and osteoconductive nature of PTG suitable for bone regeneration.

RoyaSabetrasekh et al in 2011[37] compared the biocompatibility, cell growth and morphology, pore diameter distribution, and interconnectivity of a novel titanium dioxide (TiO_2) bone graft substitute granules with three different commercially available bone graft granules, Natix(PTG), Straumann Bone Ceramic, and Bio-Oss.

The cell viability and proliferation, porosity, interconnectivity, open pore size, and surface area-to-volume ratio of $TiO_{(2)}$ granules were significantly higher than commercial bone granules (Bio-Oss and Straumann Bone Ceramic). These results indicate that the TiO2 and Natix bone graft substitutes have adequate morphologic properties; pore size and interconnectivity favored regeneration and may consequently outstrip the clinical performanceshown by both BoneCeramic and Bio-Oss. These findings further added fame to PTG.

IV. Summary:

Thus, the available evidence emphasizes that PTG's are a novel non-resorbable and genuinely osteoconductive bone graft substitiute. Also, the WPTG's so called oxidized form of these granules further demonstrated anti-inflammatory activity by reducing TNF-α levels. However not yet extensively explored regarding its use the biomaterial renders interest and is supported on the basis of innovative ideas that may beclinically important in the future. The graft material being the same as the implant material i.e both being titanium is an added advantage for the successful out come.

Though researchers had a safe and worthy journey using Porous Titanium Granules (PTG's) in diverse clinical situations, further trials with large sample size and randomized studies are required for accepting this material. PTG is still in the initial phase of clinical usage.

References:

[1]. Hegdeus Z. The re-building of the alveolar process by bone transplantation. Dent. Cosmos 1923, 65; 736-742.
[2]. Klokkevold, PR, Jovanovic, SA (2002). "Advanced Implant Surgery and Bone Grafting Techniques". In Newman, Takei, Carranza. Carranza's Clinical Periodontology (9th ed.). Philadelphia: W.B. Saunders. pp. 907–8.
[3]. Freidlaender GE. Immune responses to osteochondral allografts: Current knowledge and future directions. ClinOrthop 1983;174:58-68.
[4]. Biomedical Applications of Titaniumand its Alloys .C.N. Elias, J.H.C. Lima, R. Valiev, and M.A. Meyers. Biological Materials Science. JOM • March 2008
[5]. M. B. GorbetandM. V. Sefton, "Biomaterial-associated thrombosis: roles of coagulation factors, complement, platelets and leukocytes," Biomaterials, vol. 25, no. 26, pp. 5681–5703, 2004.
[6]. Nandi SK, Kundu B, Datta S, De DK, Basu D. The repair of segmental bone defects with porous bioglass: An experimental study in goat. Res Vet Sci 2009;86:162-73.
[7]. J. Hong, A. Azens, K. N. Ekdahl, C. G. Granqvist, and B. Nilsson, "Material-specific thrombin generation following contact between metal surfaces and whole blood," Biomaterials, vol. 26,no. 12, pp. 1397–1403, 2005.
[8]. L. M. Bjursten, L. Rasmusson, S. Oh, G. C. Smith, K. S. Brammer, and S. Jin, "Titanium dioxide nanotubes enhance bone bonding in vivo," Journal of Biomedical Materials Research .Part A, vol. 92, no. 3, pp. 1218–1224, 2010.
[9]. Wohlfahrt J C, Monjo M, Rønold H J, Aass A M,Ellingsen J E, Lyngstadaas S P. Porous titaniumgranules promote bone healing and growth inrabbit tibia periimplant osseous defects. Clin OralImplants Res 2010; 21: 165–173.
[10]. BrynjolfurJonsson&Bengt M Joberg. Surgical treatment of depression fractures of the lateral tibial plateauusing porous titanium granules. Upsala Journal of Medical Sciences. 2009; 114: 5254
[11]. Leif Holmberg, LillemorForsgren, Lars Kristerson. Porous Titanium Granules for Implant Stability and BoneRegeneration – a Case Followed for 12 Years.Upsala J Med Sci 113 (2): 217–220, 2008.
[12]. Alffram P-A, Bruce L, Bjursten LM, Urban RM, Andersson GBJ (2007). Implantation of the femoral stem into a bed of titanium granules using vibration. A pilot study of a new method for prosthetic fixation in 5 patients followed for up to 15 years. Upsala J Med Sci 112: 175–81.
[13]. Thomas M. Turner, Robert M. Urban, Deborah J. Hall,Gunnar B. J. Andersson. Bone Ingrowth Through Porous Titanium Granulate Around a Femoral Stem. Histological assessment in a six-month canine hemiarthroplasty model. Upsala J Med Sci 112 (2): 191–197, 2007
[14]. BrynjolfurJonsson&Bengt M Joberg. Surgical treatment of depression fractures of the lateral tibial plateau using porous titanium granules. Upsala Journal of Medical Sciences. 2009; 114: 5254
[15]. Lucas H Walschot, Barend W Schreurs, NicoVerdonschot, and Pieter Buma. The effect of impaction and a bioceramic coating on bone ingrowth in porous titanium particles. A bone chamber study in goats. ActaOrthopaedica2011; 82 (3): 372–377
[16]. Bystedt, H, Rasmusson L. Porous titanium granules used as osteoconductive material for sinus floor augmentation: a clinical pilot study. Clin Implant Dent Relat Res 2009; 11: 101–105.
[17]. Lambert F, Lecloux G, Léonard A, Sourice S, Layrolle P, Rompen E.Bone regeneration using porous titanium particles versus bovine hydroxyapatite: a sinus lift study in rabbits. Clin Implant Dent Relat Res. 2013 Jun;15(3):412-26.

[18]. Vandeweghe S, Leconte C, Ono D, Coelho PG, Jimbo R. Comparison of histological and three-dimensional characteristics of porous titanium granules and deproteinized bovine particulate grafts used for sinus floor augmentation in humans: a pilot study. Implant Dent. 2013 Aug;22(4):339-43.
[19]. Verket A, Lyngstadaas SP, Rasmusson L, Haanæs HR, Wallström M, Wall G, Wohlfahrt JC. Maxillary sinus augmentation with porous titanium granules: a microcomputed tomography and histologic evaluation of human biopsy specimens.Int J Oral Maxillofac Implants. 2013 May-Jun;28(3):721-8.
[20]. Claffey N, Clarke E, Polyzois I, Renvert S: Surgical treatment of peri-implantitis. J ClinPeriodontol2008; 35(Suppl. 8): 316–332.
[21]. Davies, J.E. (2003) Understanding peri-implant endosseous healing. Journal of Dental Education67: 932–949.
[22]. Osborn, J.F. &Newesley, H. (1980) Dental implants: materials and systems. In: Heimke, G.,ed. European Society for Biomaterials. Symposium(1979: Heidelberg Germany). 112–113. Mu¨nchen: Hanser.
[23]. Wilke, A., Endres, S., Griss, P. &Herz, U. (2002)Cytokine profile of a human bone marrow cellculture on exposure to titanium-aluminium-vanadium particles. Zeitschrift fur Orthopadie undIhreGrenzgebiete140: 83–89.
[24]. Torgersen, S., Gjerdet, N.R., Erichsen, E.S. & Bang,G. (1995) Metal particles and tissue changes adjacent to miniplates. A retrieval study. ActaOdontologicaScandinavica53: 65–71.
[25]. Wohlfahrt J C, Aass A M, Rønold H J, LyngstadaasS P. Micro CT and human histological analysis of a peri-implant osseous defect grafted with porous titanium granules: a case report. Int J Oral Maxillofac Implants2011; 26: e9–e14.
[26]. Mann M, Parmar D, Walmsley AD, Lea SC. Effect of plastic-covered ultrasonic scalers on titanium implant surfaces. Clin Oral Implants Res2012:23:76-82.
[27]. Bashara H, Wohlfahrt JC, Polyzois I, Lyngstadaas SP,Renvert S, Claffey N. The effect of permanent grafting materials on the preservation of the buccal bone plate aftertooth extraction: an experimental study in the dog.Clin. Oral Impl. Res. 23, 2012, 911–917.
[28]. Mijiritsky E, Yatzkaier G, Mazor Z, Lorean A, Levin L. The use of porous titanium granules for treatment of peri-implantitis lesions: preliminary clinical and radiographic results in humans. Br Dent J. 2013 Mar;214(5):E13. doi: 10.1038/sj.bdj.2013.222.
[29]. Andreas Thor. Porous Titanium Granules and Blood for Bone Regeneration around Dental Implants: Report ofFour Cases and Review of the Literature - A case report. Case Reports in Dentistry. Volume 2013, Article ID 410515, 7 pages.
[30]. Tavakoli M, Moghareabed A, Farsam T,Abbas FM, Badrian H, Khalighinejad N. Evaluation of dental socket healing after using of porous titanium granules: Histologic and histomorphometric assessment in dogs. Dent Res J 2012;9:600-6.
[31]. Delgado-Ruiz RA, Calvo-Guirado JL, Abboud M, Ramirez-Fernandez MP, Mate-Sanchez JE, Negri B, Won A, Romanos G. Porous titanium granules in critical size defects of rabbit tibia with or without membranes. Int J Oral Sci. 2014, 6.
[32]. Verket A, Lyngstadaas SP, Rønold HJ, Wohlfahrt JC.Osseointegration of dental implants in extraction sockets preserved with porous titanium granules- an experimental study.Clin.Oral Impl. Res. 00, 2012, 1-9.
[33]. Bashutski, J.D., D'Silva, N.J. & Wang, H.-L. (2009)Implant compression necrosis: current understanding and case report. Journal of Periodontology 80: 700–704.
[34]. Wohlfahrt JC, Aass AM, Rønold HJ, Heijl L, Haugen HJ, Lyngstadaas SP. Microcomputed tomographic and histologic analysis of animal experimental degree II furcation defects treated with porous titanium granules or deproteinized bovine bone.J Periodontol. 2012 Feb;83(2):211-21.
[35]. Wohlfahrt JC, Lyngstadaas SP, Heijl L, Aass AM. Porous titanium granules in the treatment of mandibular Class II furcation defects: a consecutive case series. J Periodontol. 2012 Jan;83(1):61-9.
[36]. Gholami GA, Kadkhodazadeh M, Ardakani MR, Tehranchi M, Aghaloo M, Mashhadiabbas F. Histologic and histomorphometric evaluation of bone substitutes in experimental defects. Res J BiolSci 2010;5:465-9.
[37]. Sabetrasekh R, Tiainen H, Lyngstadaas SP, Reseland J, Haugen H.A novel ultra-porous titanium dioxide ceramic with excellent biocompatibility. J Biomater Appl. 2011 Feb;25(6):559-80.