BIOGLASS, A NEW TREND TOWARDS CLINICAL BONE TISSUE ENGINEERING

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ABSTRACT

(It is submitted that the list of the published articles available on the Pubmed database were extracted using the key words "Osteogenesis and Bioglass" on 3rd April, 2015 followed by extraction of the full text articles from different sources and then thorough review of all the articles was done in 4 months' time period (from April to July 2015) to reproduce this manuscript. Authros).

Bioglass also called a bioactive glass has an inherent osteogenic potential, thus, provide new strategies to regenerate diseased or lost bone with minimum exposure to multiple materials.

This article covers the systematic review of all the research done on bioglass and osteogenesis since 2007 till present on PubMed based on the eligibility criteria.

The main objectives of the study were to evaluate the latest trend of bioglass research, to determine its osteogenic potential and to comprehend its possible clinical applications.

Increasing trend is observed towards the in vivo research of bioglass for its osteogenic potential and effective clinical applications. In the field of dentistry, the use of bioglass is identified in quick healing and regeneration of intrabony defects especially the periodointium with a potential application in periodontology and maxillofacial surgery. Bioglass is a more potent and cheap alternative to bone implantation and transplantation with minimum side effects and efficient replacement with body's own new regenerated tissue.

INTRODUCTION

Bioactive glasses are surface reactive glass-ceramic biomaterials which are investigated extensively for its use as a biocompatable implant materials in the human body to repair and replace diseased/damaged bone tissue. Larry Hench and Colleagues at the University of Florida first developed these materials in the late 1960s. Bioglass constitute synthetic bone graft materials. These are available to surgeons in a particulate form, putty form and porous scaffolds. These are being investigated in many forms, in particular as porous 3-D scaffolds.

Bioglass alone or in composite form assessed for its osteogenic potential in different scenarios. Most of the research regarding the osteogenic potential of bioglass is carried out in the past 10-15 years according to published studies on pubmed as evident from the graph, Fig 1. In the graph, the arrow on the bar (2013-2015) shows an increasing trend towards the research of bioglass for its osteogenic potential as it only covers the publications on pubmed from 2013 till 2014.

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METHODOLOGY

At Army Medical College, NUST, the literature was thoroughly reviewed systematically using the search term 'osteogenesis AND bioglass' in PubMed with a limitation to PubMed-registered papers published. Using the key words "osteogenesis AND bioglass" a list of all the published studies available on PubMed was extracted on 02/04/2015 and it revealed a total of 66 studies. Screening of 59 studies since April 1997 was done, out of which 39 studies were short-listed for review and analysis due to the raising trend of research in this field during the last 10 years (2006-2015). In this paper 21 papers were included and 18 papers were excluded on the basis of following criteria:

Inclusion Criteria

a) Studies which promoted biocompatibility and bioactivity.

b) Studies in which enhanced osteoblastic activity was observed with bone formation.

c) Studies in which osteogenesis was induced with minimum inflammation.

d) Studies in which bony defects were healed with new bone formation.

Exclusion Criteria

a) Studies where osteogenesis didn't occur were excluded.

b) Studies where the focus was on properties other than osteogenic potential of bioglass.

c) Studies where osteogenesis halted or decreased due to some factor.

d) Articles which could not be accessed were excluded.

RESULTS

Conclusive Remarks

i) The trend of research on bioglass for its osteogenic potential has increased many folds especially in the last 10 years.

ii) Bioglass has an inherent osteogenic potential.

iii) The osteogenic potential of BG can be improved by using 3D, porous and interconnected scaffolds.

iv) Mesenchymal stem cells augmentation of BG scaffolds does not enhance its osteogenic potential.

v) Further animal usage tests and clinical trials needed to bring it into dental clinics.

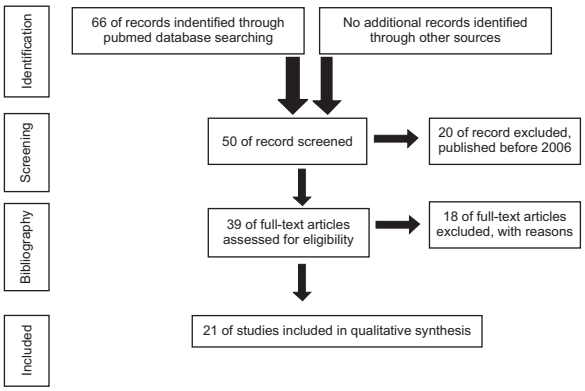

Fig 1: Flow diagram

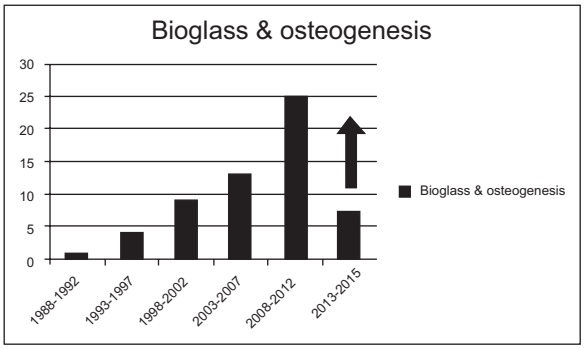

Fig 2: Articles published in PubMed on Bioglass AND osteogenesis, 2nd April 2015

DISCUSSION

In 1981 the first in vivo study regarding the osteogenic potential of bioglass was published on pubmed.[22] The trend towards exploring bioglass for its osteogenic potential started to develop in late 90's. In the past 10 years the trend of in-vivo studies regarding the osteogenic potential of bioglass had increased many fold as evidenced from the graph in Fig 1. Out of the 39 published in-vivo studies, 14 studies were based on in vitro, culture tests, 18 studies focus on in vivo, animal implantation tests and only three in vivo, clinical trials. Different materials were composited with bioglass in an attempt to enhance its osteogenic potential. In some cases bioglass scaffolds were augmented with stem cells to facilitate bone growth. Satisfactory results showing significant bone formation in suitable time were observed in most animal implantation tests and a few clinical trials, directing the potential of more clinical trials to establish its clinical use.

Bioglass is an excellent bioactive material for bone regeneration. Initially bioglass particles were coated on the surface of various bone implants and in vivo animal implantation studies were carried out to evaluate any improvement in osteointegration in bioglass coated implants. The silica coated Bioverit II specimens showed improved osteogenic rate and intensity along minimal inflammation.[21] Pure hydroxyapatite (HAp) and a biphasic calcium phosphate were used to make porus struts with bioglass. Beta-TCP/bioglass-based implants proved superior to HAp/bioglass implants.[15]

Different substances have been composited with bioglass in different studies overtime to enhance its osteogenic potential including borate[7], calcium sulphate[23], hydroxyapatite[15] and polymers.[16] Bioglass is available in the form of 3D porous scaffolds, putty-form and injectable form with polymeric carriers and require surgical placement into bony defect site where it gradually resorb with new bone ingrowth.[12,13,19] By increasing the porosity of 3D bioglass scaffolds, the inherent osteogenic potential of bioglass is multiplied and the resultant bone formation is enhanced.

In healing of bony defects, bioglass composites have been shown to exhibit improved biocompatibility and osteogenesis. In vitro culture study of novel borate BG exhibited excellent cytocompatability with mouse osteoblasts[7] but the osteogenic potential of boron modified bioglass in vivo implantation study remained same as normal 45S5 bioglass.[14] Further in vivo animal implantation tests, simulating clinical scenarios were carried out to assess the qualitative tissue response to various BG composites. Mesoporous BG/silk scaffolds induced osteogenesis in local osteoporotic defects.[2] Similarly, Polylactic acid/BG scaffolds exhibited good biocompatibility and induced osteogenesis with minimum

TABLE 1 : DATA OF STUDIES FOCUSING ON THE OSTEOGENIC POTENTIAL OF BIOGLASS.

Citations	Type of study	Therapeutic agent	Time taken	Reason for inclusion	Conclusive Remarks
Eldesoqi, 2014 #35[1]	Comparative study: rat model, calvarial defec	Composite material, polylactic acid (PLA) and 20% or 40% bioglass (BG20 and BG40). Control: PLA scaffold	3 months	Biocompatable. Induce qualitative osteogenesis with minimum inflammation.	Further in vivo/ usage tests required.
Cheng, 2013 #36[2]	In vivo study Rat models: biomaterial-based approach.	3D scaffolds, BG/silk & mesoporous BG/silk. Control: pure silk scaffolds.	2-4 weeks.	MBG/silk scaffolds act as potential substitute for treating local osteoporotic defects.	Further in vivo/ usage tests required.
Mladenović, 2014 #37[3]	In vitro culture study on mouse osteoclasts via calvarial bone resorption assay & osteoclast formation assays.	BG, BG dissolution extracts and Si containing cell culture medium.		Si exhibit stimulatory effects on osteoblasts & inhibitory effects on osteoclasts.	Further usage tests required.
Li, Lei et al. 2013[4]	Usage tests on white rabbit models with porous bioactive bone cement (PBC).	(W/W%) PMMA to BG to chitosan, PBC I (50: 40:10), PBC II (40:50:10), and PBC III (30:60:10).	3 months / 6 months post-surgery	PBC II & PBC III show > osteogenesis . Better biocompatibility than PMMA	Further usage tests required.
El-Gendy, Yang et al. 2012[5]	In vitro culture and in vivo implantation study in mice. Histological and immunohistochemical analyses.	Culturing human dental pulp stem cells(HDPSCs) in monolayers & on 3D Bioglass® scaffolds followed by intraperitoneal implantion in mice.	Culture: 2/4 weeks. Implantation: 8 weeks.	HDPSCs with 3D 45S5 Bioglass scaffolds, promote bone-like tissue formation.	Usage tests needed.
Shigeishi, Takechi et al. 2012[6]	Clinical trial. 59 year old female. Panoramic radiographic evaluation	One-stage implant integration with right maxillary sinus floor augmentation with mixture grafts from the cortical bone and IP-CHA.	33 months	IP-CHA, potential scaffold for osteoprogenitor cells.	Further Clinical trials needed.

Wei, Zhang et al. 2011[7]	In vitro study using cultures.	The novel borate bioglass. Osteoblasts from mouse were cocultured with extracts, alpha-MEM medium served as control group.	extract time of 0-24 hours & 24-48 hours.	Excellent cytocompatibility, which plays regulatory effects on the cell proliferation, secretion, & migration.	potential for clinical application
Kumar, Kumar et al. 2011[8]	A pilot study. Split mouth study design. Osteogenesis assessed via CT scan.	10 patients were treated either with open flap debridement alone or with new composite alloplast(HA, BG, Calcium phosphate) implantation.	3-6 months	The new composite alloplast resulted in better treatment outcomes.	Promise better clinical outcomes in treatment of aggressive periodontititis.
Xu, Su et al. 2011[9]	In vitro, cultures of rat mesenchymal stem cells(rMSCs) and in vivo implantation studies. Rat models. SEM analysis.	A novel biomimetic composite scaffold Bioglass-Collagen-Phosphatidylserine (BG-COL-PS) → freeze-drying technique. rMSCs seeded on scaffolds & cultured.	21 days cell culture. 6 weeks implantation.	The BG-COL-PS/MSC constructs enhanced the efficiency of new bone formation than pure BG-COL-PS scaffolds or BG-COL/MSC constructs.	BG-COL-PS scaffolds have the potential to be applied in orthopedic & reconstructive surgery.
Xie, Yu et al. 2010[10]	in vivo implantation studies. Rabbit models histologic and histomorphometric studies.	Gradient coatings composed of bioactive glass and nanohydroxyapatite (BG-nHA) on titanium-alloy orthopaedic implants and surrounding bone tissue in vivo.	4, 12, 24 weeks.	BG-nHA gradient coatings enhance the osteointegration of orthopaedic implant.	Further usage tests required.
Zhang, Wang et al. 2009[11]	Comparative usage study. Histological evaluation. Rat models.	Bone repair process in calvarial defects using bioactive glass (BG); calcium sulfate barrier (CSB); BG/CSB; and autogenous blood clot (control).	After 90 days osteoconductance observed.	The bioactive glass covered with calcium sulfate barrier association presented a better osteoconductive capacity when compared to isolated materials.	Calcium sulphate coatings on BG promote osteoconduction.

Nandi, Kundu et al. 2009[13]	Bone implantation test. Goat models.	Porous BG scaffold	90 days	Bone formation over the entire extension of the defect independent of size of block in comparison to control group.	Porous bioglass scaffolds are potential orthopedic implants.
Gorustovich, López et al. 2006[14]	Usage test Bone implantation test. Rats.	Particles of boron-modified 45S5 BG (45S5.2B) implanted into the intramedullary canal of rat tibiae. Control: 45S5 BG.	15-30 days	Boron-modified 45S5 BG (45S5.2B) enhance osteogenesis initially.	Further clinical trials required
Ghosh, Nandi et al. 2008[15]	Usage test Bone implantation test. Bengal goats.	Pure hydroxyapatite (HAp) and a biphasic calcium phosphate used to make porus struts with bioglass.		Beta-TCP/bioglass-based implants superior to HAp/bioglass implants.	Clinical trials needed.
Mylonas, Vidal et al. 2007[16]	In vivo, implantation test. Dogs.	The combination of a polymeric carrier with a granular scaffold (bioglass or HA/TCP) allowed for the delivery of allogeneic mesenchymal stem cells(MSCs).	4-7 weeks.	MSCs enhanced bone formation at early stages of alveolar repair. Final result similar.	Clinical trials needed
Reilly, Radin et al. 2007[17]	Comparative study using Rat & human MSCs cultured on BG.	Alkaline phosphatase osteogenic markers assessed		BG induced bone growth in human patients is independent of MSCs differentiation	Further in vivo studies needed.
Tsigkou, Hench et al. 2007[18]	Comparative study using fetal osteoblasts cultured on bioactive resorbable composite films	Poly-D,L-lactide (PDLLA) matrix & 45S5 BG particles at 3 different concentrations (0% (PDLLA), 5% (P/BG5), & 40% (P/BG40).		BG incorporation enhanced osteoblast proliferation, differentiation & mineralization.	Bioglass has osteoinductive potential
Tsigkou, Hench et al. 2007[18]					

Jones, Tsigkou et al. 2007[19]	In vivo culture study	Human osteoblasts cultured on porous 3D scaffolds formed from 70S30C composition.	3 weeks	Mineralized bone formed without any growth factors.	Ideal bone scaffolds
Wang, Lu et al. 2011[20]	Comparative study.	Sheep Implantation in spinal bony defects.	6-12 weeks.	NovaBone Putty, had > bone content than the NovaBone, both of which were significantly > than the empty control.	Further clinical trials needed to establish efficacy of Novabone putty.
Vogt, Brandes et al. 2008[21]	Usage tests. A histological study. Plain bioverit II → control.	Mice. Bioverit II implants coated with a nanoporous silica layer in a mouse ear model.	2, 6, and 12 weeks	The osseogenic rate & intensity increased in coated Bioverit II specimens. Excellent biocompatibility (no inflammation).	Further clinical trials needed.

inflammation1, where as Calcium sulphate coatings on bioglass promoted better osteoconduction in bone repair process.[12]

Silica, the main constituent of bioglass has duel effect in osteogenesis, i.e. it stimulates osteoblasts and inhibits osteoclasts, thus, promoting bone formation.[3] Wang et al. 2011[20], performed a comparative study of two commercially available bioglass products. Following 6-12 weeks of implantation in spinal bony defects of sheep, NovaBone Putty, showed greater bone content than the NovaBone, both of which were significantly greater than the empty control. Further clinical trials needed to establish efficacy of Novabone putty.

Porous bioactive bone cements(PBC) with greater BG content showed greater osteogenesis and better biocompatibility than PMMA alone, so may reduce the fracture risk of adjacent vertebrae after vertebroplasty.[4] Porous bioactive glass scaffolds are potential orthopedic implants as they exhibited bone formation over the entire bone defect in 90 days.[13] Thus, directing the need of further in vivo investigation regarding osteogenic potential of various porous BG composite scaffolds and there possible applications in orthopedics.

In dentistry, our prime interest is the replacement of periodontium especially the alveolar ridge with new bone formation, to restore function and esthetics. Some animal usage tests using bioglass scaffolds and its composites targeted to establish the potential use of bioglass to replace the lost alveolar bone in cases of chronic periodontitis.[15] Kumar, Kumar et al. 2011[8], performed a pilot study using split mouth design, 10 patients were treated either with open flap debridement alone or with new composite alloplast (Hydroxyapetite, Bioglass, Calcium phosphate) implantation. Better treatment outcomes were observed with new composite allopast in aggressive periodontititis. In this regard a few bioglass products are launched in the market namely Novabone and Novabone putty.[20]

In tissue engineering, mesenchymal stem cells in different carriers have been used extensively in vivo studies to find the most suitable and effective way to replace the lost tissues with new tissues. And in many studies quiet encouraging results were obtained.[5] Similarly, considering the osteogenic potential of bioglass, many studies are performed in which porous bioglass scaffolds were augmented with mesenchymal stem cells to assess the rate of bone formation and the quality of resultant bone formed.[19] Bioglass scaffolds with or without stem cell augmentation and growth factors gave same results in most studies indicating that bioglass is a selfsufficient osteogenic material and doesn't need stem cells for improved osteogenesis.[16]

CONCLUSION

In vivo studies using cultures in laboratory and implantation tests in different animals lead to the establishment of bioglass as an efficient osteogenic material with inherent osteoinductive and osteoconductive potential, thus proving it to be a highly bioactive

material. Bone formation occurs with minimum inflammation and immunological response, catagorizing it as a highly biocompatible material. So, 3D, highly porous scaffolds can be safely used to treat intra-bony defects, osteoporotic orthopedic defects, aggressive periodontitis etc via bone regeneration.

In dentistry, limited use of bioglass as bone regenerative material is encountered in periodontology and maxillofacial surgery to repair the bony defects. Further clinical trials are needed for its potential use as a bone regenerative material under different clinical scenarios.

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