International Journal of Innovative Medicine and Health Science, Vol. 4, 2015, 86-93

Whites Science
A Scientific Erudition

NOVEL INNOVATIONS IN BONE GRAFT SUBSTITUTES FOR PERIODONTAL REGENERATION

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ABSTRACT

Periodontitis is a disease that is characterized by the destruction of periodontal tissues. It is well established that clinical or surgical interventions are a mandatory step in the re-establishment of the health of the periodontal tissues. The advent of newer biomaterials has widened the available treatment options and has enhanced the long term prognosis of teeth with periodontal pathosis. Biomaterial Science is the confluence of physical and biological aspects of the material science. Biomaterials include bioinert, bioactive and bioresorbable materials. They are derived from vital or non vital bone sources and are composed of organic or inorganic materials. Most of these biomaterials possess structural, mechanical and biofunctional limitations and are also influenced by patient variables like age, defect size and compliance for their success. This article reviews the various advances in biomaterials and their applications in periodontal therapy.

KEY WORDS: Allogenic grafts, Alloplasts, Autogenous bone grafts, Biomaterials, Periodontitis, Xenogenic grafts.

INTRODUCTION

Periodontitis is a disease that is characterized by the destruction of periodontal tissues.[1] If left untreated, it results in progressive attachment and bone loss leading to loss of teeth eventually. It is well established that clinical or surgical interventions are a mandatory step in the re-establishment of the health of the periodontal tissues. The advent of newer biomaterials has widened the available treatment options and has enhanced the long term prognosis of teeth with periodontal pathosis.

Biomaterial Science is the confluence of physical and biological aspects of the material science. As we navigate into the 21st century, the scope of biomaterials has enlarged and is incorporated into medicine, dentistry and biotechnology.[2] This has widened the purview of its applications in the field of Periodontology.

Biomaterials include bioinert, bioactive and bioresorbable materials. They are derived from vital or non vital bone sources and are composed of organic or inorganic materials. They tend to interact with the oral environment and also function to replace diseased or damaged tissue.[3] These materials are generally evaluated based on their osteogenic, osteoinductive, osteoconductive or osteopromotive potential. Implantation of graft materials, whether natural or synthetic, results in a host response which may be at the tissue, cellular and molecular level due to their interaction with the recipient tissue. These effects are chiefly governed by the morphology, chemical composition, porosity and particle size of the material.

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AUTOGENOUS BONE GRAFTS

It is harvested from the patient's own body which is an ideal material because of its osteoconductive and osteoinductive properties as it contains a source of osteoprogenitor cells. The autogenous bone can be derived from both intraoral and extra oral sites. It is still considered the gold standard by which other grafting materials are compared.[4]

Even though autogenous bone is still the standard, the relatively limited amount of conveniently available autogenous bone (especially from intraoral sites), resultant patient morbidity, need for second surgical site and the harvest time involved in obtaining these grafts, have led the clinicians to utilize other bone replacement grafts. These limitations led to the

development of allografts and alloplasts as alternative grafting materials.

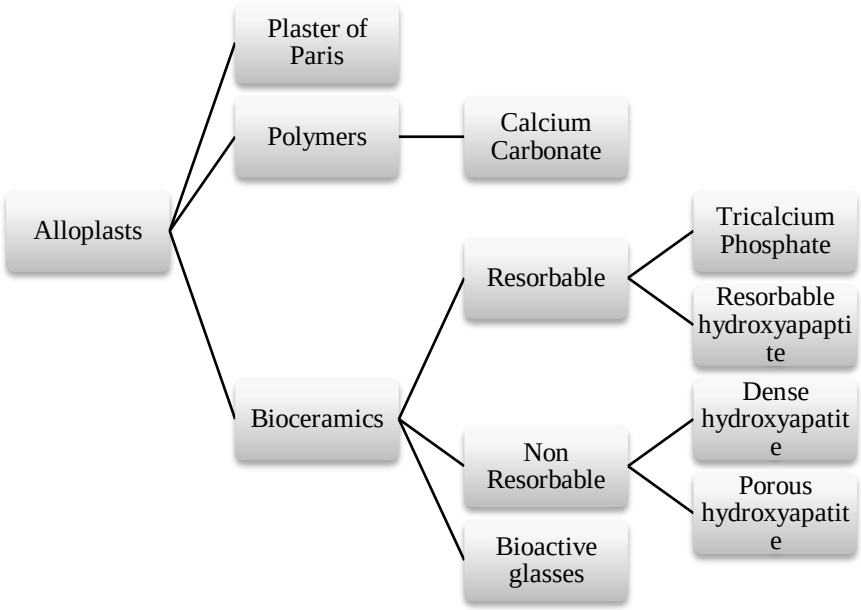

Fig 1. Various Alloplasts used

ALLOGENIC GRAFTS (ALLOGRAFTS)

The need for an allogeneic source of bone arose from the need for increased quantity of the donor material and the problems associated with autogenous bone procurement.[5,6] Bone allografts are obtained from cadavers or from patient's living relatives or non relatives. The most commonly used forms of allografts are fresh frozen, freeze-dried (lyophilized) bone allograft (FDBA) and demineralized freeze-dried bone allograft (DFDBA).

MINERALIZED FREEZE-DRIED BONE ALLOGRAFTS

Mineralized freeze-dried bone allograft (FDBA) was introduced to periodontal therapy in 1976.[7] Freeze-drying partially distorts the three-dimensional presentation of human leukocyte antigens on freeze-dried bone allografts,[8] thus reducing the health risks. It is both an osteoconductive and osteoinductive material. It is available as cortical or cancellous granules of various sizes, as well as in block form. The recent biomaterials include:

a) **MinerOss®** is a mixture of allograft mineralized cortical and cancellous chips. The cancellous and cortical blend forms an osteoconductive scaffold providing volume enhancement and effective site development for successful dental implant placement, ridge and sinus augmentation and periodontal defects. Its particle size ranges from 600-1250µ.

b) **Raptos** is a combination of cancellous and cortical allograft which acts as an osteoconductive scaffold for promoting bone regeneration. The particle size of this material varies between 250 to 2000 µm. It can be used in periodontal osseous defects.

c) **MinerOss® Cancellous** is a mineralized allograft cancellous bone particle. The osteoconductive properties along with the fast remodeling time allow for rapid revascularization in sinus augmentation, socket grafting and periodontal defects. The particle size of this material varies between 300-1000 microns.

d) The **MinerOss® Block Allograft** restores bone volume and provides an alternative to harvesting an autogenous block graft from the patient therefore eliminating the need for a second surgical procedure. It is used in bone remodelling procedures and in block grafting procedures.

e) The open trabecular structure of cancellous particles of **Puros Cancellous Allograft** is a natural bone mineral structure and collagen matrix. This supports for cell attachment and bone remodelling. It provides an ideal environment for rapid revasculariization leaving behind healthy, natural bone and hence is helpful in periodontal bone, furcation defects and also in sinus augmentation.

DEMINERALIZED FREEZE-DRIED BONE ALLOGRAFTS

Urist and co-workers showed through numerous animal experiments that demineralization of a cortical bone graft induces new bone formation and greatly enhances its osteogenic potential.[9,10] Demineralization with hydrochloric acid exposes the bone inductive proteins located in the bone matrix.[11] These proteins are collectively called bone morphogenic proteins (BMP).[12] A major concern with allografts in general is the potential for disease transfer, particularly viral transmission, and even more particularly human immunodeficiency virus (HIV). The various commercially available products include:

a) A demineralised bone matrix with a high surface area incorporating a highly compatible 30% poloxamer reverse phase medium carrier is **Accell Connexus Putty**. It has osteoinductive potential and on placement of this material, bone regeneration is about 4 to 6 months.

b) A composite graft having properties of osteoinduction and osteoconduction is **DynaBlast™ Paste or Putty**. It is used in sinus lift procedures, implant dehiscence defects, moderate localized ridge defects and extraction site repair. The presence of cancellous chips in this graft material act as a natural scaffold to encourage the attachment of osteogenic precursor cells and the time taken for bone regeneration is around 8 to 12 months.

c) A graft material which promotes natural bone formation by stimulating the proliferation and transformation of mesenchymal cells to osteoblasts is **DynaGraft-D Putty or Gel.** It has an osteoinductive potential and the bone regeneration takes around 8 to 12 months. It is used in sinus lift procedures, periodontal defects, implant site development, extraction site repair and coronal defects around immediate implant.

d) A biocompatible demineralized bone derived Type – I collagen used for bone space filling purposes is **Osseomold**. It is osteoconductive as well as osteoinductive and has a natural cohesiveness to form sticky putty like consistency which can be easily placed and molded to the periodontal defect space.

e) A sterile, high-safety allograft product, derived from human donor bone, processed by the cells and tissue bank Austria is the **Maxgraft®.** It has osteoconductive properties supporting natural and controlled tissue remodelling. The high biologic regeneration capability of **Maxgraft®** results in a predictable clinical outcome in furcation defects, implant dehiscence and intraosseous defcts.

f) **Gintuit** is an allogenic cultured keratinocytes and fibroblasts in bovine collagen. It is an allogenic cellularized scaffold product. It is indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults. It is available as a ready-to-use circular cellular sheet, 0.75 mm in diameter and approximately 0.75 mm thick, consisting of human keratinocyte and fibroblast cells, human extracellular matrix proteins, and bovine collagen.

g) A biocompatible demineralized bone derived Type – I collagen for bone defects is **Osseograft**. The material is both osteoinductive as well as osteoconductive. It resorbs in 6 to 12 weeks. It has a natural cohesiveness to form a sticky consistency and can be easily placed to accommodate the shape.

h) **Grafton® DBM** in multiple forms preserves the bone height and width and it has been used widely in bone grafting procedures like ridge and sinus augmentation, filling of periodontal defects.

An allograft cellular bone matrix retaining native mesenchymal stem cells (MSCs) and osteoprogenitor cells is the **Osteocel**. It provides all three components for bone formation i.e. osteoconductivity (cancellous scaffold), osteoinductivity (MSC growth factor production and demineralized cortical bone) and osteogenicity (MSCs and osteoprogenitor cells). It mimics biologic profile of autograft. Osteocel shows high vital bone content at 16 weeks, with very low residual graft material. It is used in ridge augmentation.

ALLOPLASTS

These materials are synthetically derived, biocompatible and non-organic. Their purpose is to substitute for autogenous bone. Based on their porosity, they can be classified as dense, macroporous or microporous and they can be either crystalline or amorphous. They can also be granular or molded. Alloplasts typically degrade by solution mediated resorption. In general, these materials exhibit good compressive strength but poor tensile strength similar to properties of bone. The various alloplasts used are depicted in Fig 1.

Plaster of Paris was one of the early alloplasts to be used. It is a simple, inexpensive, stable and readily available material for use in filling cavities in bone.

The recent advances in alloplasts include:

a) A medical grade calcium sulfate hemihydrate which is completely synthetic, biocompatible, biodegradable, osteoconductive, as effective as a GTR barrier, safe, simple to use and non-toxic is **DentoGen**. It is unique among bone graft materials in that it possesses hemostatic, angiogenic and barrier membrane properties. It is used to provide a resorbable barrier over other bone graft materials and along with implants to improve their osseointegration.

b) Microcrystalline calcium sulfate is converted to grains of calcium sulfate (size range 200 to 900 nm), which are tightly compressed together to form granules in sizes ranging from 400 to 1000 µ. This unique microscopic structure imparts unique properties to the **NanoGen** which undergoes controlled degradation over a period of 12 weeks as compared to 4 to 6 weeks for traditional calcium sulphate and hence robust bone regeneration is observed in the infrabony defects and sinus augmentation.

Polymer grafts

Proplast is a material prepared from two polymer families i.e. polymer tetrafluoroethylene and pyrolytic graphite. It was used as an implant material and in three wall osseous defects. Due to its inherent difficulties Proplast is of questionable value for correction of periodontal osseous defects.

Hard Tissue Replacement polymer (HTR)

Bioplant HTR polymer is a biocompatible micro porous composite of polymethyl methacrylate (PMMA), polyhydroxyethyl methacrylate with a calcium hydroxide graft surface. The mechanism of action is via osteoconduction. It is used in bone (ridge) maintenance, by preventing the anticipated loss of alveolar bone following extraction, preserving the height and width of the alveolar ridge and in repair of periodontal and other bony defects.[13-15]

Bioceramic alloplasts are comprised primarily of calcium phosphate, with the proportion of calcium and phosphate similar to bone. The two most widely used forms are tricalcium phosphate and hydroxyapatite.

Tricalcium phosphate (TCP) is a porous form of calcium phosphate. The most commonly used form is β-tricalcium phosphate. It is similar to hydroxyapatite, but is not a natural component of bone material. The mechanism of action is similar to other resorbable alloplasts: osteoconduction and resorption, with gradual replacement by host bone. The varied products available include:

a) **Cerasorb** is a β tricalcium phosphate material that has been used in bone defect regeneration in the entire skeletal system. Although highly porous, this material is stable and highly resistant to abrasion. Generally, a round particle size of 10 to 63 µm prevents phagocytosis by macrophages.

b) **Sybograf T** is a nano sized bioceramic material synthetically prepared using a novel patented biomimetic technology available in powder form. It is bio compatible, non pyrogenic, non toxic and non allergenic. It is osteoconductive and can be moulded to desirable shapes. It is indicated in periodontal bony defects and alveolar augmentation before implantation.

c) **Mastergraft® Mini Granules** are resorbable ceramic granules used alone or in combination with autograft to provide bone void filler that is resorbed/remodelled and is replaced by host bone during the healing process. It is used in sinus lifts, alveolar ridge augmentation and periodontal defects.

Biphasic Calcium Phosphates

Hydroxyapatite (HA) and beta tricalcium phosphate may be combined in various ratios into a single product, known as biphasic calcium phosphate (BCP). The rationale for this combination is to take advantage of the differential resorption rates of the two materials, achieving a balance between long term stability and support (HA) and more rapid dissolution and bone ingrowth (TCP).

a) **Ossifi** is a synthesized combination of hydroxyapatite and β-tricalcium phosphate. It is extremely biocompatible and highly osteoconductive. When it is placed in a periodontal bone defect, it only occupies 10% of the defect space leaving 90% of the space for regeneration of new bone. It is used in periodontal regeneration.

b) **Eclipse synthetic granules** are a unique ratio between micro and macro porosity and the combination of hydroxyapatite and beta calcium phosphate. This material contains 80% β- TCP and 20% HA. It is used in periodontal defects, ridge augmentation, osseous defects, sinus lift procedures and extraction site repair.

c) Biphasic calcium phosphate synthetic material composed of rounded granules in hydrophilic polymer solution is known as **MBCP GEL™.** The granules are 80 to 200 µm and are composed of 60% HA, 40% β-TCP and 45% HPMC (hydroxypropyl methylcellulose) synthetic polymer. It is used in periodontal and peri implant defect.

d) **Maxresorb®** is a safe, reliable and fully synthetic bone graft substitute. The homogenous composition of 60% hydroxyapatite (HA) and 40% beta-tri-calcium phosphate (β-TCP) results in two mineral phases of activity which supports the formation of new vital bone, maintains the volume and mechanical stability over a long time period. It is indicated in sinus floor elevation, ridge preservation and in furcation defects.

e) A unique and highly innovative, injectable bone graft paste with improved controlled resorption properties is the **Maxresorb® inject**. The unique four-phasic homogenous composition of gel, active hydroxyapatite and granules of 60% HA and 40% β-TCP forms four activity phases. It is used in horizontal ridge augmentation, intraosseous defects (1-3 walls) and furcation defects (class I-II).

f) **Perossal®** is a synthetic, osteoconductive and resorbable bone graft substitute. It is a composite of nanocrystalline hydroxyapatite and calcium sulfate. The nano- and micro-porous network offers the possibility to load the bone graft substitute individually with liquids (e.g. antibiotics) and provides the property of a controlled prolonged release. It is used in intraosseous defects (1-3 walls) and furcation defects (class I-II).

Hydroxyapatite (HA)

Hydroxyapatite, $Ca_{l0}(PO_4)_6(OH)_2$, is the primary mineral component of bone. Synthetic hydroxyapatites are available in a variety of forms, primarily as a porous nonresorbable, a dense or solid nonresorbable, and a resorbable (non-ceramic, porous) form. The various commercially available biomaterials include:

a) **Sybograf** is a synthetic nanocrystalline hydroxyapatite prepared using a novel patented biomimetic process technology available in different forms. This material is non toxic, non allergenic, non pyrogenic, bioresorbable, osteoconductive and can be moulded into required shapes. It is indicated in periodontal bony defects and alveolar augmentation before implantation.

b) A synthetic nanocrystalline hydroxyapatite with collagen which efficiently improves tissue regeneration is **Sybograf C**. The collagen is derived from fish origin. It is indicated in periodontal bony defects and alveolar augmentation before implantation

c) **Sybograf Plus** is a synthetic nanocryatalline hydroxyapatite and β tricalcium phosphate composite. It is bioresorbable with a high porosity and is osteoconductive. It is also non toxic, non allergenic and non pyrogenic. It is indicated in periodontal bony defects and alveolar augmentation before implantation.

d) **Interpore 200** is a porous hydroxyapatite which is obtained by the hydrothermal conversion of the calcium carbonate exoskeleton of the natural coral genus porosities into the calcium phosphate hydroxyapatite. It has a pore size of 190 to 200 pm, which allows bone ingrowth[16,17] into the pores and ultimately within the lesion itself.[18] The clinical defect fill, probing depth reduction, and attachment gain have been reported with this material.[19]

e) **OsteoGen** is a form of synthetic hydroxyapatite. It is resorbable, particulate material processed at a low temperature with particles measuring 300 to 400 pm. It acts as a trellis for the ingrowth and subsequent deposition of new bone.

f) **OsteoTape®** is a synthetic resorbable bioactive graft, an osteoconductive non ceramic form of hydroxylapatite. **OsteoTape®** is **OsteoGen®** with a collagen resorbable bone graft matrix in porous preformed bone grafting shapes comprised of highly purified type I bovine Achilles tendon collagen, combined with crystals of the product **OsteoGen®,** a synthetic bioactive resorbable graft of the non ceramic hydroxylapatite category. It is indicated in infrabony defects and ridge preservation.

Bioactive glasses

There are two forms of bioactive glass currently available: **PerioGlas and Biogran®**. Bioactive glasses are composed of CaO, Na_2O, SiO_2, P_2O_5 and bond to bone through the development of a surface layer of carbonated hydroxyapatite.[20,21] The calcium phosphate-rich layer promotes adsorption and concentration of proteins utilized by osteoblasts to form a mineralized extracellular matrix.[22] The different sizes of the glass are 10-45 µm, 50-100 µm and 100-150 µm.

a) A synthetic particulate form of bioglass that bond to tooth bone and certain soft connective tissue is **PerioGlas**.[23] It is composed of calcium, phosphorous, silicon and sodium. It has a particle size ranging from 90 to 170 µm, which facilitates manageability and packing into osseous defects. This bioactive synthetic grafting particulate is indicated for the treatment of infrabony defects.

b) A resorbable bone graft material made of bioactive glass granules that are chemically identical to PerioGlas and are composed of calcium, phosphorous, silicon and sodium is **Biogran®.** This material has a narrower range of particle size of the purportedly critical 300 to 355 µm. it is indicated in extraction sockets and in small to medium sized bony defects.

The mechanism of action of bioglass is through osteoconduction. The turnover and resorption of bioactive glass is an area of controversy.

a) An alloplastic bone graft material made of commercially pure titanium is the **Tigran™ PTG & PTG White.** The granules are between 0.7 mm – 1.0 mm in size and its specific character: titanium, porous, irregularly shaped and non-resorbable, creates many advantages for a long term superior result. It is biocompatible. The non-resorbability contributes to the primary stability, the aesthetic result as well as the long term stability. Tigran™ PTG is intended for sinus lift and other posterior applications while Tigran™ PTG White is a supplement to Tigran™ PTG and intended to be applied in more aesthetically visible areas such as the anterior of the jaw. This material is intended to be used in sinus lift procedures with immediate installation of dental implants and in treatment of peri implant bony defects.

XENOGENEIC GRAFTS (XENOGRAFTS)

A graft exchanged between individuals of two different species usually involves a genetic difference, so great that transplantation antigens must be removed or altered.

Anorganic Bovine Bone (ABB)

Anorganic bovine bone (bovine xenograft) is a naturally derived hydroxyapatite sourced from cattle. It is an osteoconductive material. There are two processes currently used to prepare anorganic bovine bone. One process uses a low temperature, chemical extraction process to remove the organic and cellular components (**BioOss**). The other uses high temperature (>1500°C) to remove residual organics (**OsteoGraf-N, PepGen P-15**). In each case, the end result is a microporous structure composed of natural hydroxyapatite.

a) An anorganic bovine bone that has been chemically treated to remove its organic component is the **Bio-Oss**. It is osteoconductive and overtime, the graft undergoes physiologic remodelling and becomes incorporated with the surrounding bone.

b) A bone graft material which contains both large and small sized granules and is used in lateral sinus floor elevation, large and small defects is **Bio-Oss Pen®.** The **Bio-Oss** granules can be placed more easily with a **Bio-Oss Pen.** It is delivered with a curved applicator tip. The pen allows easy moistening of the granules with either sterile physiological saline solution or patients blood. It reduces the procedure time as the pen is pre filled with Bio-Oss granules. The pen ensures optimal bonding of the granules.

c) A popular example of microporous hydroxyapatite particulate material is **OsteoGraf/N** derived from bovine bone available in two varieties – **OsteoGraf/N300**, which has particles ranging from 250 to 420 µm, and **OsteoGraf/N700**, which has particles ranging from 420 to 1000 µm. The small-particle variety has been used to treat ridge defects with good results. OsteoGraf/N has been widely used in combination with DFDBA for sinus augmentation.

d) A highly reliable, dimensionally stable, safe bone graft which is derived from the mineral phase of bovine bone and also shows a maximum resemblance to human bone (surface, porosity and chemical composition) is **Cerabone®.** It is indicated in sinus floor elevation, furcation defects (class I-III) and in fenestration defects.

e) An enhanced form of bovine-derived hydroxyapatite that contains an added synthetic short-chain peptide, P-15 is **PepGen P-15**. It is the first and only biomimetic of autogenous bone. It demonstrates an increased expression of growth factors[24] and provides an appropriate environment for bone. It has also shown a significantly higher reduction in probing depth and gain in attachment level as compared to another biomaterial Bio-Oss.[25]

f) **Bioplant** is bovine bone that is prepared by detergent extraction, chloroform methanol extraction to reduce lipid content, sterilization in propiolactone, and freeze drying.

Coral and Algae Derived Hydroxyapatite (HA)

Coralline HA is a naturally derived graft material prepared from sea coral. Coralline HA promotes bone formation via osteoconduction.

a) **Interpore 200** is a porous coralline hydroxyapatite. It is essentially composed of pure hydroxyapatite and some tricalcium phosphate. It has been used as an implant graft that provides a matrix for bone ingrowth, as an onlay graft for the alveolar ridge and as an interpositional implant in the mandible.[26]

b) Another resorbable porous coralline graft material is **Biocoral**. It is a natural coral in the form of aragonite (more than 98% calcium carbonate) that is not altered by processing. The size and shape of the particles facilitate ease of handling and manipulation during surgery.

c) **Phycogene HA** is derived from calcified marine algae and is a very open structured material with interconnected honeycomb-like pores presenting a very high surface area. It is believed to be more rapidly resorbable than coralline HA.

d) **C-Graft** has been used successfully for more than 10 years for grafting and remodelling bone.[27] It is an inorganic, biocompatible calcium phosphate material derived from calcium-encrusted sea algae, which are processed in order to develop an apatite material that is analogous to bone apatite. It has a granular size range of 300 to 2000 µm. This material has an interconnecting microporosity that guides hard and soft tissue formation and can be very effective for filling tooth extraction sites and bone defects.

CONCLUSION

Bone grafting is now an established form for treatment of periodontal osseous defects. Most of these biomaterials possess structural, mechanical and biofunctional limitations and are also influenced by patient variables like age, defect size and compliance for their success. The progression in the field of material science is phenomenal progressing from macro particles to nano particles. These rapid developments are gradually leading us towards the ultimate goal in periodontal therapy, which is the regeneration of lost periodontal tissues. Although complete periodontal reconstruction is still a distant dream, the use of novel bone grafts with highly evolved modifications incorporated into them, have surely propelled us towards this direction.

ACKNOWLEDGEMENTS

The authors would like to express gratitude to all those who contributed to this piece of work.

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