Review

Comparative studies on bone graft alternatives for common spine fusion procedures and focus on bioceramics

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SUMMARY: *To improve a solid spinal fusion while avoiding morbidity of autograft harvesting procedures, numerous alternatives have been investigated during years, among which allograft, demineralized bone matrix, cell-based therapies and growth factors (i.e. bone morphogenetic proteins, platelet concentrates) and ceramic-based biomaterials. Even though all these approaches being potentially able to improve the outcomes of spinal fusion procedures, most of them have not been yet validated by evidence-based clinical results, thus resulting as poorly advisable for clinical use, furthermore particularly expensive. Here, we give an overview of the current clinical evidences for bone graft alternatives for spine surgery procedures. We will also evaluate the pros and cons of their use and briefly review the more relevant literature currently published.*

KEY WORDS: *Bioceramics, Spine surgery, Synthetic bone grafts.*

INTRODUCTION

Spinal fusion is one of the most common surgical procedures for treating conditions of the spine including deformity, trauma, degenerative disc disease and spondylolisthesis, where removal of the damaged anatomical structure is required[25].

Removal of such tissue results in mechanical instability of the spine, whereas the main goal of spinal fusion surgery is to fuse two or more vertebras, by inducing bone growth in-between such segments. Its use has dramatically increased over the last decades[12], with impacts on health care systems and on patients' quality of life.

Various techniques have been reported for the achievement of an adequate bone healing and solid fusion, including different surgical approaches, graft materials used and instrumentation method. However, despite numerous advances in spinal fusion procedures, pseudo arthrosis still occurs in about 25-35% of cases[32].

Additionally, patient- and treatment-associated factors, such as age, osteoporosis, number of levels treated, use of instrumentation or interbody grafts and surgical approach, influence the success of fusion[28,34]. As result, the research on new techniques to increase the success of spinal fusion and reduce pseudo arthrosis is strongly increasing.

Among the possibilities, ICBG and local autograft (spinous processes, laminae, facets, ribs) are still con-

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Progress in Neurosciences 2021; 6 (1-4): 43-51. *ISSN: 2240-5127.*

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LIST OF ACRONYMS AND ABBREVIATIONS: **β-TCP** = Beta-TriCalcium Phosphate; **AIS** = Adolescent Idiopathic Scoliosis; **ALIF** = Anterior Lumbar Interbody Fusion; **BMA** = Bone Marrow Aspirate; **BMPs** = Bone Morphogenetic Proteins; **DBM** = Demineralized Bone Matrix; **FGF** = Fibroblast Growth Factors; **HA** = HydroxyApatite; **HIV** = Human Immunodeficiency Virus; **ICBG** = Iliac Crest Bone Graft; **IGF** = Insulin Growth Factor; **LIF** = Lumbar Interbody Fusion; **Mg** = Magnesium; **MHA** = Mg-enriched HydroxyApatite; **MSCs** = Mesenchymal Stem Cells; **PLIF** = Posterior Lumbar Interbody Fusion; **PLF** = Posterior Lumbar Fusion; **rhBMP-2** = recombinant human Bone Morphogenetic Protein-2; **SiCaP** = Silicate-substituted Calcium Phosphate; **TGF** = Transforming-Growth Factor; **TLIF** = Transforaminal Lumbar Interbody Fusion; **XLIF** = eXtreme Lateral Interbody Fusion.

sidered the "gold standard" choices for bone replacement, due to the osteoconductive and osteogenic properties[25,50].

ICBG is mainly composed of cancellous bone obtained from the inner table of the pelvis. This type of bone graft shows a trabecular structure and a large surface area, which allows to mesenchymal stem cells and bone forming growth factors to be incorporated, an easy revascularization and a rapid incorporation to the host site[49], together with no risks of host rejection or infections and excellent fusion rates. However, patient finite supply, donor-site morbidity, acute or persistent pain[14,26] and adverse events (i.e., haematoma and infections, pelvic fracture, nerve palsy) are some of the most common related drawbacks which can affect patient quality of life, occurring in as many as 25-30% of patients[24,53]. Other additional drawbacks are longer operative times, increased estimated blood loss and longer hospital stay, which can increase risk for life-threatening complications (i.e. infections, deep vein thrombosis). These aspects have led to an increase in the development and use of bone graft substitutes and biological agents to achieve fusion. Depending on their properties, bone grafts augment natural healing via osteoinductive, osteoconductive and/or osteogenic mechanisms, mimicking the main properties of the human bone[39].

In this perspective, the present review is to give an overview of the current best evidence for bone graft alternatives, mimicking natural bone, in spinal surgery, and to review the most relevant literature.

□ ALLOGRAFT

Allograft has been used as alternative to autologous bone, in order to reduce autograft-related drawbacks[19]. National trends point to decreased utilization of autograft (86 to 10%) with a reciprocal increase in allograft (14 to 59%) from 1998 to 2004[44].

Allograft can be collected from either living or non-living donors and must be processed within a bone tissue bank. It requires sterilization (gamma-irradiation), with detrimental effects on mechanical properties of bone and deactivation of proteins normally found in healthy bone. As such, it is osteoconductive and weakly osteoinductive (growth factors may still be present, depending on the processing). Concerns on the potential infective risks, despite the use of strong aseptic techniques for allograft sterilization, and potential risks of contaminations are possible, although nowadays with very low risk rates. Contaminants and pathologies that may be transferred include bacterial infections, malignancy, systemic disorders (autoimmune disease), and toxins[19]. In particular, HIV and Hepatitis C virus transmission have also been reported, with a risk rate of 1:1.6 million[29,37,41]. In spine surgery, only one case of HIV transmission has been reported. The limits of such transplants are costs, difficult procedure (tissue processing, harvesting), mechanical resistance (in freeze dried and irradiated), limited osteoinduction and risk of infection.

□ DEMINERALIZED BONE MATRIX

DBM is the result of allograft decalcification (residual calcium < 5 %). Introduced since the early 1980s, this technique allows for the production of collagen matrix, non-collagenous proteins and growth factors (i.e. BMP, IGF, TGF, FGF), which can replicate the three-dimensional architecture of bone, therefore promoting and assisting the host cell invasion[7,17,27,39,45,50]. Due to the presence of bone-forming growth factors (such as BMPs, IGF, TGF, FGF), DBM also features osteoinductive properties, which allow progenitor cells growth and differentiation, and the induction of vascularisation. Compared to autograft or allograft, DBM lacks of donor-site related morbidity and shows excellent handling properties. However, the lack of the mineral component is associated with low mechanical strength. Despite the presence of numerous literature data on DBM effectiveness in preclinical studies on

posterolateral spinal fusion[9,38,42,58], there are still limited evidences and also variable results produced in clinical studies to support the use of DBM as a stand-alone bone substitute[22,52,57]. This variability might be due to the lack of standardized processes for production, such as the particle size[15], along with donor-related issues, which results, above all, in BMP-2 and BMP-7 variations among different commercially available lots, or even in different batches from the same manufacturer[3].

□ SYNTHETIC BONE GRAFTS

The history of synthetic materials starts in the early '900, when D.E. Robertson assayed a piece of cat's bone and a piece of human bone for bone grafting into dogs. The microscopic analysis of implanted graft after 20 days showed that the space between graft and the living bone was filled with new cancellous bone. These early works made the premises for the development of the bone grafts[1].

When compared to allografts, autografts and xenografts, synthetic grafts ahow some advantages, such as the possibility of unlimited number/quantity, a safety profile without risks of disease transmission, pain limitation by elimination of some secondary surgical intervention.

As reported by Ficai et al.[2], synthetic bone grafts can be divided in four categories, according to their evolution period (Table 1).

First generation bone grafts evolved in the second part of 1900, having remarkable mechanical properties but no resorbable nor bioactive properties. These first-generation bone grafts had limited lifetime (usually less than 10-15 years) and needed to be extracted and surgically replaced. Second-generation bone grafts were at least bioresorbable or bioactive and they did not require to be replaced in time. The most representative biomaterials from this second generation are represented by calcium phosphates (especially hydroxyapatite and tricalcium phosphate), bioglasses, alumina, zirconia, etc.

Third-generation bone grafts have been developed as bioresorbable and bioactive with superior properties, strongly influenced by the nature of components, the composition and the morphology. The most representative biomaterials of the third-generation of bone grafting biomaterials are: (nano)hydroxyapatite/collagen, (nano)hydroxyapatite/collagen/hyaluronic acid, hydroxyapatite/poly-L-lactic acid, etc.

The fourth-generation bone graft biomaterials have been developed with similar features of the former generation, but with an improvement in presence of bony cells, growth factors, bone morphogenetic proteins etc. One of the most important features of new bone grafts is osteointegration, which is strictly related to the degree of porosity and pore size of the scaffold.

As natural bone is mainly made of hydroxyapatite and collagen, many synthetic bone grafts have developed as biomaterials made of hydroxyapatite, β-TCP and also (nano)hydroxyapatite/collagen composite for hard tissue repairing (Table 2).

Hydroxyapatite, a naturally occurring mineral form of calcium apatite with the formula $Ca_5(PO_4)_3(OH)$, is a crystalline calcium phosphate that is also manufactured as a ceramic through a sintering process. Because of the apatite structure of bone tissue, synthetic apatites are the most widely studied of all CaP phases. Stoichiometric HA (Ca/P ratio = 1.67) is a mineral composed of calcium ions, phosphate ions, and hydroxyl groups.

Because of this close similarity with the mineralized

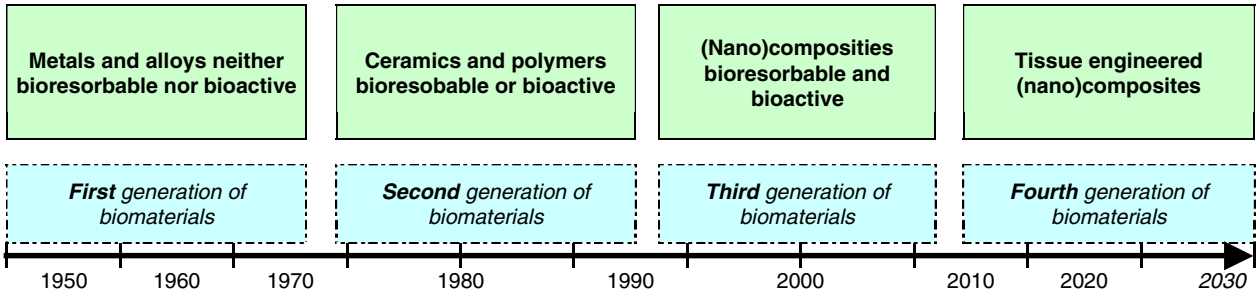

Table 1. Biomaterials evolution in the field of bone grafts (*modified from Ficai A et al., Andronescu E, Voicu G, Ficai D. Advances in collagen/hydroxyapatite composite materials*[2]).

Components	wt%
Mineral phase	
Hydroxyapatite	60-66
Carbonate (mostly as carbonated hydroxyapatite)	~ 4
Citrate	~ 0.9
Na^+	~ 0.7
Mg^{2+}	~ 0.5
Others	Traces
Organic phase	
Collagen	20-25
Non- collagenous proteins: (osteocalcin, osteonectin, osteopontin, sialloprotein, BMP)	2-3
Others	Traces
Water	8-9

Table 2. Composition of a healthy bone (*modified from Ficai A et al., Andronescu E, Voicu G, Ficai D. Advances in collagen/ hydroxyapatite composite materials*[2]). *Legend:* wt% = weight percentage.

phase of bone, HA shows high biomimetic properties, osteoconductive potential and excellent biocompatibility. The porous architecture of the HA substratum, with its macropore network and its micropore interconnections, induces rapid vascular and mesenchymal invasion and provides a specific cell flow. These cells can attach, proliferate, and finally differentiate into functional osteoblasts. The osteoconductive property of HA has made this material of relevant interest, being able to sustain new bone formation independently by the implantation site. As the new bone tissue incorporates the scaffold material, the scaffold itself should be biodegradable either through cellular events or as a result of the surrounding environment[43,54]. Ions substitution enhances HA unstability and biological activity, promoting rapid cell-mediated material resorption, new bone formation and remodelling[46]. As such, the design and development of a new generation of synthetic resorbable apatite substitutes has been stimulated to mimic some properties (chemical composition and three-dimensional architecture) of the biological phase to overcome most of the limitations typical of stoichiometric HA implants. Magnesium is certainly one of the most important bivalent ions associated with biological apatite, being one of the most abundant minerals in the human body and approximately 50% of Mg^{2+} is naturally present in the composition of bone tissue. Mg^{2+} enables the HA crystal cell structure to become unstable and more biologically active, promoting rapid cell-mediated material resorption, new bone formation and remodelling by cross-talking with progenitor cells at the molecular level[11,35,36]. Conversely, Mg^{2+} depletion affects all stages of skeletal metabolism, causing cessation of bone growth, decrease in osteoblastic activities, osteopenia and bone fragility. For all these reasons, Mg-HA has become of great interest in the development of effective bone substitutes[11,36]. Non-stoichiometric HA-based bone substitutes therefore provide an osteoconductive scaffold in which chemotactic cells and circulating proteins (e.g. mesenchymal stem cells, osteoinductive growth factors) can migrate and adhere, and into which progenitor cells can differentiate into functioning osteoblasts[48]. In vitro experiments revealed an active interaction between Mg-HA biomaterials and human MSCs, with an increased cell metabolic activity[6,40].

□ FINDINGS OF BIOCERAMICS IN ARTHRODESIS PROCESURES

In order to enhance or replace the function of autologous bone in spinal fusion it is relevant to use materials that are similar to autograft. Due to their intrinsic nature hydroxyapatite and / or tricalcium phosphate-based bioceramics have a chemico-physical characterization and a morphology more similar to bone than other materials and / or synthetic products.

Clinical studies carried out in spinal applications have shown good results on the use of hydroxyapatite in different formulations, as a stand-alone or mixed with autologous bone.

In the past, Korovessis et al.[33] showed HA bone bridging at 3 months post-op and radiological fusion 1 year postoperatively. The use of hydroxyapatite over the decorticated laminae, which represents a wide host area that offers much more bone chips from decortication, was followed by solid dorsal fusion within the expected time.

The use of HA combined with β-TCP and BMA was evaluated in a study by Bansal and colleagues[4] for posterolateral applications. At 12 months follow-up, radiological graft incorporation and fusion was evident in all the patients treated.

More recently, a meta-analysis of all randomized

controlled trials published with a comparison on the effectiveness and safety of all available bone grafts in the different applications (PLF, PLIF, LIF, ALIF, TLIF, XLIF) has been carried out in 2019 by Feng and colleagues[16]. Among all the bone graft alternatives available, the Authors reported that synthetic ceramic materials (i.e. β-TCP, hydroxyapatite), used in combination with autograft local bone, show increased fusion rate, as compared to their use as stand-alone in all spinal applications. Additionally, they showed decreased frequency of complications, as compared to other alternatives (i.e. ICBG, rhBMP-2 or SiCaP).

Chang and colleagues[8] reported the same results when analyzing bone graft substitutes to be used in minimally invasive lumbar surgery; ceramics used as extenders to local autograft showed a fusion rate of about 86% in both posterior and anterior/lateral approaches, which is in line with what reported for open spine procedures[47].

In interbody fusion procedures, fusion rate and surgery-related factors affecting lumbar fusion were discussed by Formica and colleagues in their meta-analysis[18]. The Authors, who analized 67 studies (all belonging to level IV and III of evidence), reported an overall fusion of about 87% when ceramics (β-TCP, HA) where used. These results are in line with papers published years before by Thalgott[56] (2002), which reported a 94% of fusion in ALIF with HA and cages, or by Thaler[55] in 2013, which more recently showed good clinical outcomes at one-year follow-up in PLIF treated with ceramics and bone marrow aspirate. HA with β-TCP was also evaluated by Ransford[51] and Chou[10] in anterior cervical fusion and adolescent idiopathic scoliosis, which showed similar fusion rates as compared to the use of autologous bone, with fewer donor site complications.

In a recent study, Giorgi and colleagues evaluated the use of an HA-based biomaterial in form of chips mixed to autologous bone for PLF[20]. Results showed the incorporation of the HA chips into the fusion mass with formation of mature bony trabeculae and no sign of pseudo arthrosis. Moreover, new tissue formation in the interspaces between the vertebral bodies was evidenced.

In AIS, Delecrin et al.[13] performed a clinical study with 58 patients undergoing dorsal scoliosis correction of the spine column using instrumentation plus local bone graft combined with either iliac crest bone graft or hydroxyapatite and tricalcium phosphate. The results were assessed clinically at 4 years follow-up. Patients in the ceramic group showed lower average blood loss than those in the iliac graft group. They also were free from postoperative local complications in the iliac region, which were experienced by a significantly high proportion of patients belonging to the iliac graft group.

In degenerative scoliosis, a new generation hydroxyapatite biomaterial made of type I collagen fibrils with biomimetic MHA in aqueous media showed to promote bone regeneration and to assist new bone formation[21,30,31], in particular when applied in those procedures requiring huge amounts of bone graft available for the treatment of long spinal segments. Interestingly, a case-report recently published on the same biomaterial highlighted the osteointegrative properties of the device[23]. This is not common, as it almost never happen to review a patient previously operated at the spine. In this case, a bar broke and this led to the possibility of histologically examining a sample from where the bone graft biomaterial was placed, confirming the complete osteointegration of the device with no residuals in the biopsy fragment. A good bone tissue remodelling, due to ongoing osteogenic processes of the bone

In a prospective study published this year[5], twenty patients undergoing instrumented posterolateral spinal fusion using a biomimetic hydroxyapatite composite scaffold (enriched in magnesium and collagen) were radiographically evaluated at 12 months follow-up. The percentage of bony fusion was of about 95%, with no intra-operative or post-operative adverse events were recorded, providing clinical evidences of the fusion properties in posterolateral spinal fusion of the collagen-based HA scaffold employed.

All these results confirm that during years bone graft evolution allowed for the development of biomaterials able not only to provide three-dimensional structural support, but also, with chemical properties, to support bone ingrowth and tissue remodelling. Cumulative data from different materials used in spinal fusion are reported in Table 3.

Biomaterials have been reported, where possible, as commercial name.

In general, despite a generally low methodological quality across all the studies, overall results showed similar fusion rates among the different biomaterials, with no significant difference among each other. Even products with low clinical data available, or with recent history on the market, show good performance in terms of fusion rates achievable.

Product	Number of studies	Total patients	Number fused	Fusion rate (%)	Range (%)
Beta tricalcium phosphate (Vitoss; Stryker, Kalamazoo, USA)	7	345	319	92.5	85-100
Calcium sulfate (Osteoset; Wright Medical Technology, Memphis, USA)	6	353	306	86.7	45.5-92.4
Tricalcium phosphate/hydroxyapatite (BCP-BiCalPhos; Medtronic Sofamor Danek, Memphis, USA)	4	152	127	83.6	74.6-92.5
Coralline hydroxyapatite (Pro-Osteon 200, Pro-Osteon 500; Biomet, Warsaw, USA)	7	168	146	86,9	52.6-100
Type I collagen/hydroxyapatite (Healos; Depuy Synthes, Warsaw, USA)	5	97	83	85.6	77.3-95.5
Apatite-wollastonie-containing glass ceramic	2	36	36	100,0	NA
Dense hydroxyapatite block	1	26	25	96.2	NA
Synthetic hydroxyapatite (Bongros; Daewoong Bio Inc., Seoul, Korea)	1	45	39	86.7	NA
Silicate-substituted calcium phospahte	1	49	38	77.6	NA
Silikated hydroxyapatite (Actifuse; Baxter, Deerfield, USA)	1	39	31	79.5	NA
Hydroxyapatite-biocative glass (Chitra-HABg; Sree Chitra Tirunal, Trivandrum, India)	1	22	1	4.5	NA
Porous hydroxyapatite chips (Engipore; FinCeramica, Italy)	1	36	33	90.8	89.4-94.1
Type I collagen/hydroxyapatite (RegenOss; FinCeramica, Italy)	3	81	71	88.3	80.0-95.0

Table 3.Fusion rate by product.

□ DISCUSSION

Bone harvest from iliac crest causes complications such as morbidity in the donor site, postoperative pain, hematoma, infections and increased blood loss with a frequency of 25-30% of patients; as h, the need to identify alternative sources to autologous bone has pushed research to the development of different biomaterials as bone grafts for achieving arthrodesis.
The increasingly frequent alternative to autologous bone graft is represented by bioceramic-based synthetic bone substitutes. Even within the limiting data reported in terms of statistical evidence, the literature highlights the excellent behavior of synthetic bone graft substitutes in comparison to autologous bone. In general, the resulting analyses evidenced that, despite a generally low methodological quality across all the studies, overall results demonstrated fusion rates and functional outcomes to be comparable between the considered bone graft extenders and iliac crest bone graft group, confirming the safety and efficacy of these materials in spinal fusion procedures. Among all the biomaterials available, hydroxyapatite in particular is recommended as bone graft substitute with close similarity to the human bone, when combined with rigid internal fixation for necessary support.

□ CONCLUSIONS

In conclusion, the use of ceramic derivatives as bone graft extenders is recommended to provide fusion. Despite the difficulties in evaluating the presence of new bone ingrowth with clinical tests (x-ray or CT scan may be unclear in determining whether the fusion masses represent new bone formation or the presence of an unfused ceramic mass), patients have shown good outcomes with the use of ceramics such as tri-calcium phosphate or hydroxyapatite. As such, their use is indicated as alternative to autologous and allograft bone, and as solution to avoid drawbacks related to withdrawal invasive procedures. In particular, hydroxyapatite is recommended as bone graft substitute when combined with rigid internal fixation for necessary support. Of note, all the studies reported the use of instrumentation as an adjunciton to the fusion procedure. In addition of all the osteoconductive bone graft extenders investigated, pooled quantitative analyses suggested that β-TCP and HA plus local autograft bone produced the most successful fusion rates, as compared to iliac crest bone graft.
In general, the resulting analyses highlight that, despite a generally low methodological quality across all the studies, overall results demonstrated fusion rates and functional outcomes to be comparable between the considered bone graft extenders and iliac crest bone graft group, confirming the safety and efficacy of these biomaterials in spinal fusion procedures.

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Disclosure*. The Authors declare they have no financial or other conflict of interests in relation to this research ant its publication.*