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What bone graft substitutes should we use in post-traumatic spinal fusion?

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ABSTRACT

Surgical treatment of spinal fractures consists of postural reduction and segmental arthrodesis, together with an eventual performance of spinal canal decompression. Spinal arthrodesis consists of the combination of a hardware system for mechanical stabilisation together with a biological substance for enhancement of bone formation. To date, autologous graft is the only biological substance demonstrated to possess osteogenic properties. Cancellous bone graft has greater cellular activity than cortical graft, whereas cortical graft is stronger. Consequently, according to biological and biomechanical properties of autograft, spinal posterior arthrodesis is better enhanced by cancellous autograft, whereas anterior interbody tricortical bone is more suitable for anterior fusion. Allograft does not cause harvesting complications as autograft does, and also its amount is theoretically unlimited; nevertheless the rate of bone fusion facilitated by allograft is far from that enhanced by autograft given that allograft has no osteoprogenitor cells. There is little evidence on the efficacy of demineralised bone matrix for spinal fusion. Bone morphogenetic proteins (BMPs) are in use in spinal surgery, but their exact role with respect to type, dose, and carrier, together with their cost-effectiveness, need further clinical delineation. Calcium phosphate compounds appear to be good as carriers; however, they have no osteoinductive or osteogenic properties. Current clinical literature seem to indicate their usefulness for bony fusion in spinal surgery, when combined with bone marrow aspirate or used as an extender for autologous bone graft. Age, length of fusion, location, and concurrent diseases should be definitive for fusion outcome; papers on spinal arthrodesis should neatly stratify these variables. Unfortunately, since that is not the rule, conclusions drawn from current literature are very unreliable. Autograft remains the gold standard, and cancellous bone is advisable in posterolateral approaches, whereas tricortical iliac crest autograft appears appropriate for interbody support. In longer segments, its expansion with BMPs looks safe at least. Basic knowledge has been achieved from animal experiments, and clinical application of the findings to humans should be done very cautiously; in any case, both anterior and posterior arthrodesis must be protected with instrumentation used according to appropriate biomechanical principles. A combination of failure of the correct graft together with proper instrumentation will result in poorer outcome, even if the right graft is used.

Introduction

Although many controversies still exist about when and how to treat spinal fractures,[68,89,90,94] definite surgical treatment usually consists of postural reduction and segmental arthrodesis,[38,67,92] together with an eventual performance of spinal canal decompression.[79] Spinal arthrodesis combines a hardware system for mechanical stabilisation (biomechanics) with a biological substance for bone formation enhancement (environment).

Biomechanics

Biomechanics is a very important issue in spinal surgery; in fact, as a general concept, spinal arthrodesis is just the treatment of multiple foci of fractures once neat decortication of host bone has been carried out. Consequently correct application of any of the four main principles of osteosynthesis (compression, neutralisation, buttressing, and tension band, together with accessory bridging) plays a major role depending on the sort and position of graft used; further, not only the biology but also the biomechanical features of host bone are decisive. For a given graft, different placements may need a different type of osteosynthesis (Figs. 1–5). Therefore, provided correct stabilisation has been performed, as in any fracture

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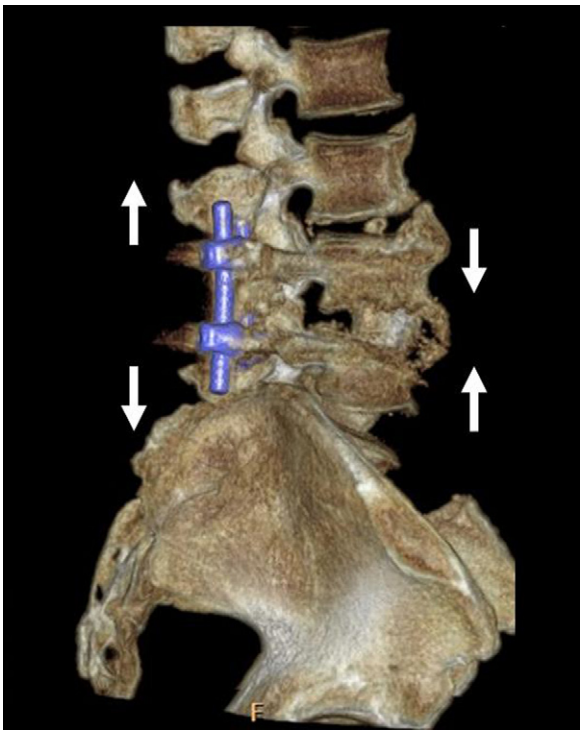

Fig. 1. 3D CT-scan, lateral view reconstruction. A 45-year-old patient with L5–S1 infectious spondylodiscitis treated with disc remotion, curettage of the proximal face of the above and below vertebral bodies, interbody tricortical autograft, and posterior pedicular screw instrumentation. The interbody tricortical autograft is under compression, and the posterior pedicular screw system provides a tension band principle. The autograft for this use cannot be cancellous bone, but a strong tricortical one.

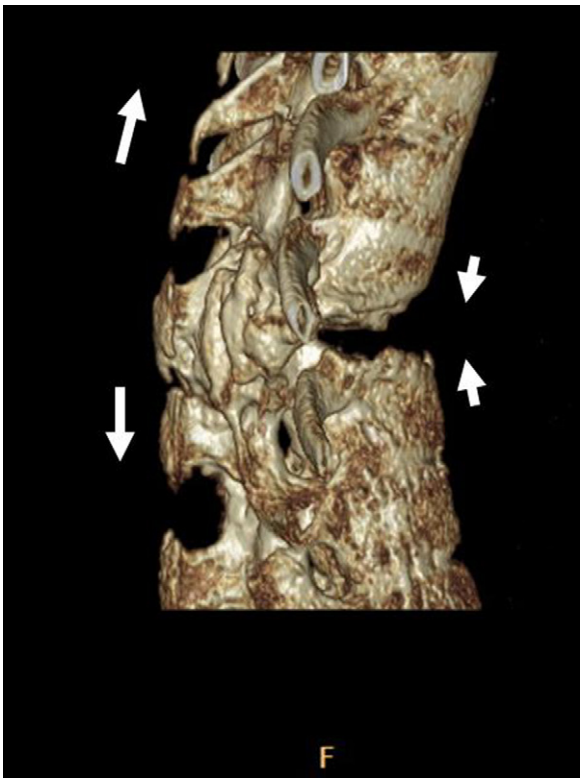

Fig. 2. 3D CT-scan, lateral view reconstruction. A 65-year-old male diabetic patient with spondylitis ankylopoietica, and under renal dialysis, sustained a T11–T12th thoracic spinal fracture after mild trauma, developing an atrophic non-union. When he was admitted to our Department, we considered that anterior flexion–posterior distraction forces could provoke complete spinal dissociation with subsequent paraplegia.

treatment, biology is of overwhelming importance. So far, there has been a long list of bone graft substitutes, and strategies for bone promotion (Table 1).[7,39,40,53,80,86]

Environment

Grafting enhances bone fusion, and that results in permanent stability avoiding late hardware breakage. The three main properties for optimum fusion enhancement are osteogenesis, osteoconduction, and osteoinduction, together with avoidance of histoincompatibility and, in the clinical setting, a favourable biomechanical situation.[6] Osteogenesis consists basically of cells differentiating into an osteogenic lineage, these being bone cells which are the only agents with osteogenetic power. Osteoinduction is also very important; molecules commonly called growth factors (GFs) induce mesenchymal stem cells (MSCs) to amplification (increase in cell population) and subsequently to differentiation into osteoprogenitor cells, especially the transforming growth factor superfamily (TGF) which also includes the well-known bone morphogenetic proteins (BMPs).[50] Osteoconduction is complementary to osteogenesis and osteoinduction; a tridimensional scaffold structure of bone or bone substitute is an indispensable scaffolding for cell population growth. An osteoconductive microstructure of 200–400 μm is nowadays very easy to manufacture. However, the doses of osteoinductive GF to be added to it are unknown; further osteogenetic properties of "bone substitutes" are unknown for osteoconductive materials, as osteogenesis is an exclusive property of mature osteoprogenitor cells.

Since bone synthesis is exclusively achieved by bone cells, a large population of osteoprogenitor cells is necessary for successful fracture or spinal fusion. Nowadays it is known that differentiated cells do not reproduce themselves, undifferentiated cells – particularly MSCs – being responsible for cell amplification and subsequent differentiation into osteogenic lineage; moreover, mature osteoblasts can revert to former less-differentiated MSCs in order to achieve amplification to increase the final population of differentiated osteoblasts.[20,41,48,56,58] During the entire process, the newly forming blood vessels that grow inside the callus act as a source of new MSCs; in fact, recent publications have given strong evidence of a perivascular origin for the MSCs.[15,17] Therefore neat decortication of host bone until bleeding becomes of overwhelming importance.

Currently, the combination of biomechanical stabilisation ensuring an appropriate environment for bone growth, osteoprogenitor bone cells for osteoid synthesis, vascularisation of the fusion site for cells and metabolite transport, signalling molecules (BMPs) to encourage cell amplification and differentiation, and scaffold for tridimensional cell growth has been denominated the "diamond concept",[31,32] as the ideal situation for fusion to take place. Therefore clinical situations lacking any of these variables are in a less than optimal situation for successful spinal fusion.

Autograft

It is accepted worldwide that autograft is the standard for spinal arthrodesis, and also whenever bone healing is required in any part of the skeleton, as its biological properties are considered to be optimum; autograft has a good volume effect, and also potent osteogenic, osteoinductive, and osteoconductive properties.[6,62] Autograft can be used in spinal surgery either as cancellous chips or as a tricortical live implant in order to improve the immediate strength of the construct. So far, no allogeneic or synthetic bone

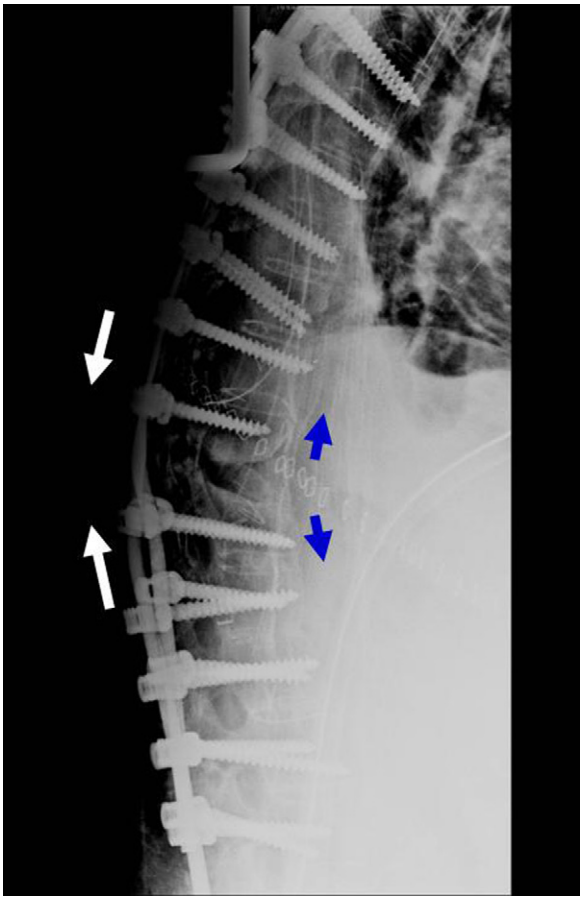

Fig. 3. The same patient as in Fig. 2. A double surgical approach was decided upon. Anterior interbody tricortical autograft under compression forces by the above and below vertebrae for buttressing flexion contention together with posterior instrumentation for withholding distraction forces was performed. Because of the very severe osteoporosis, as is common in spondylitis ankylopoietica, posterior instrumentation had to fix a very long proximal and distal segment (long tension band and neutralisation).

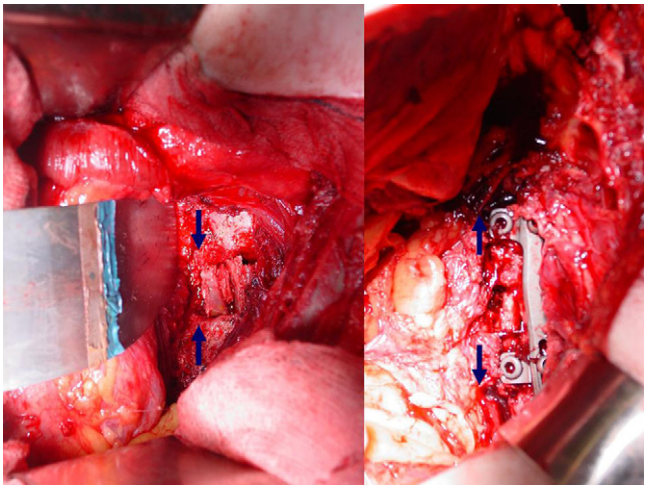

Fig. 4. A 67-year-old patient with T11–T12 infectious spondylodiscitis treated with disc remotion, curettage of the proximal face of the above and below vertebral bodies, rib autograft, and anterior plating. The autograft is not under compression, but under protection (neutralisation by the plate). Since in this case the graft is biomechanically protected by the plate, the removed rib obtained during the retroperitoneal anterior approach can be used for grafting, making unnecessary harvesting a tricortical autograft from the iliac crest.

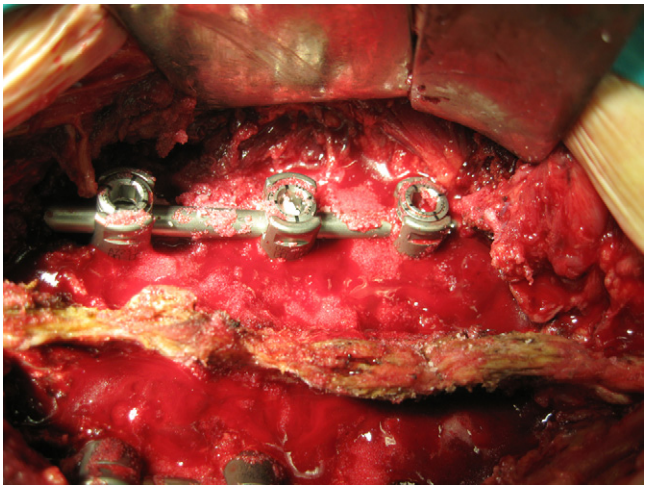

Fig. 5. A 74-year-old patient with spinal stenosis treated with L3–S1 laminectomy and foraminectomy, and L2–S1 posterior pedicular screw instrumentation. Morselised cancellous allograft has been used together with bone morphogenetic protein 7 (OP-1, Ossigraft™, Stryker, Kalmazoo, USA). In this case allograft has no biomechanics implications, but just a biological aim.

substitutes have achieved the osteogenicity of autograft, although careful autograft implantation for spinal surgery must include shortening the harvesting-to-implant interval, because these properties diminish with time.[73] Nevertheless, morbidity after autograft collection is very high, and fractures of iliac bone, particularly after tricortical graft has been harvested, with ensuing non-union are not rare.[2,3] Limited availability together with longer operative times are also the most important burdens in conventional autograft harvesting, and new, less invasive aspiration techniques for harvesting cancellous bone from femoral and tibial metaphyses by a "reamer irrigator aspirator" (RIA) apparently provide larger graft amounts than conventional iliac crest harvesting[5,45,46] and with higher concentrations of GFs[69,76]; further, RIA would cause less postoperative pain and a shorter length of hospital stay.[5] However, studies on RIA material harvesting techniques for spinal surgery are lacking.

Basic knowledge on autograft has been achieved from animal experiments, and extension of these findings to clinical application in humans is very uncertain. Cancellous bone graft has greater cellular activity than cortical, whereas cortical graft is much more dense and stronger.[21] The spongy structure of cancellous bone allows osteoprogenitor cells to have better vascularisation, developing superior osteoconduction and osteogenesis. Anyhow, although histological incorporation with prompt vascularisation and MSC invasion starts at the second day of implantation, mechanical properties of cancellous bone are compromised during the remodelling phase, taking a few months to become structurally stronger.[66] Cortical autograft, having fewer biological properties than cancellous bone, also suffers biomechanical weakening up to 75%[36] at 6–24 weeks postimplantation, returning to normal strength some 48 weeks thereafter.[26] Consequently, according to biological and biomechanical properties of autograft, spinal posterior arthrodesis is better enhanced by cancellous autograft (Fig. 5), whereas tricortical bone is more suitable for buttressing in interbody fusion, together with a posterior transpedicular screw system in order to provide a tension band principle (Figs. 1 and 3). Eventually, removed ribs for anterolateral thoracic or thoracolumbar approaches can substitute tricortical grafts; in this case osteosynthesis must provide buttressing by the graft and neutralisation by the hardware (Fig. 4). Failure in the correct combination of graft type with proper instrumentation principles will result in poorer outcome, even if the right graft is used.

Table 1
Bone substitutes for spinal fusion.

Author	Study design	Surgical procedure	Type of substitute	Outcome	Level of evidence
Platelet gels (PG)					
Carreon et al.[13]	Retrospective case–control study	Posterolateral lumbar spinal fusion	PG	25% non-union platelet + autograft vs 15% non-union with autograft alone	IV
Weiner and Walker[93]	Retrospective case–control study	Posterolateral lumbar spinal fusion	PG	18% non-union platelet + autograft vs 9% non-union with autograft alone	IV
Demineralised bone matrix (DBM)					
Sassard et al.[75]	Retrospective case–control study	Posterolateral lumbar fusion	DBM	40% non-union with autograft + DBM 34% non-union with autograft	III
Thalgott et al.[86]	Cohort study not well designed	Lumbar interbody fusion	Titanium mesh cages filled with DBM with coralline hydroxyapatite and DBM	4% non-union	IV
Girardi and Cammisa[34]	Retrospective case study not well designed	Posterolateral fusion different diagnosis	Autograft + injectible allograft DBM	100% fusion but only 1 year follow-up	IV
Cammisa et al.[11]	Multicenter prospective controlled trial	Posterolateral fusion different locations	DBM	52% non-union with autograft + DBM 54% non-union with autograft	II
Rihn et al.[71]	Multicenter prospective RCT (very small number of patients and only 1 year follow-up)	Posterolateral lumbar fusion	DBM	17% non-union with DBM 15% with autograft	II
β-Tricalcium phosphate (TCP)					
Epstein[27]	Prospective case series	Posterolateral lumbar fusion	TCP + type bovine collagen + bone marrow aspirate + local autograft	96% fusion of 1-level 85% fusion of 2-level	IV
Neen et al.[61]	Prospective case–control study. Non randomised	Posterolateral instrumented fusion and interbody lumbar fusion	Synthetic matrix: 80% type I bovine collagen and 20% hydroxyapatite compared to iliac crest autograft	93% fusion in posterolateral lumbar arthrodesis	III
Epstein[28]	Prospective case series (patients aged 70)	Posterolateral non-instrumented fusion	TCP + type bovine collagen + bone marrow aspirate + local autograft	85% fusion	IV
Dai and Jiang[19]	Prospective randomised with a control group	Posterolateral instrumented fusion	TCP + local autograft compared to iliac crest autograft	100% fusion	II
Bone morphogenetic proteins (BMPs)					
Mummaneni et al.[60]	Retrospective case–control study (not well design: very small number per group)	Posterolateral lumbar fusion	TLIF + rhBMP2 + local or iliac crest autograft compared to autograft iliac crest	100% fusion TLIF + rhBMP2 + local or iliac crest autograft 94% fusion autograft group	III
Burkus et al.[9]	Multicenter prospective randomised study	Anterior lumbar interbody fusion	ALIF (two tapered titanium threaded fusion cages) with rhBMP-2 on absorbable collagen sponge compared to iliac crest	94.5% BMP group 88.7% iliac crest group	II
Dimar et al.[24]	Prospective randomised study	Posterolateral lumbar fusion	rhBMP-2 on a compression-resistant matrix (collagen, hydroxyapatite and TCP compared to autograft iliac crest)	96% fusion in rhBMP group 89% fusion in autograft group (2 years follow-up)	II
Kanayama et al.[43]	Multicenter prospective control randomised study (histological studies by biopsy)	Posterolateral lumbar fusion	OP-1 putty compared to local autograft with hydroxyapatite–TCP granules (control)	77% in OP-1 putty group 90% in control group	II
Vaccaro et al.[88]	Multicenter prospective control randomised study	Posterolateral lumbar fusion	rhBMP-7 putty Compared to autograft	68.8% fusion in rhBMP putty group 50% fusion in autograft group (4 years follow-up)	II
Delawi et al.[22]	Prospective randomised multicenter control study	Posterolateral lumbar fusion	rhBMP-7 Compared to iliac crest autograft	63% fusion in rhBMP group 67% fusion in autograft group	II

ALIF, anterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion.

Allograft

Allograft bone has long been used as an alternative to autograft. As allograft does not cause harvesting complications, and also its amount is theoretically unlimited, it appears to be a good alternative to autograft. Nevertheless the rate of bone fusion facilitated by allograft is far from that enhanced by autograft. Although some authors have found that in instrumented posterolateral lumbar spinal fusion allograft, in the form of fresh-frozen human femoral head, gives clinical results at least as good as autograft,[33] it has been claimed that, given that it has no osteoprogenitor cells, and BMPs are scarce, bone synthesis promoted by allograft is very limited.[53] Nevertheless the role of morselised allograft as a carrier is very important. Carriers have to be easily obtained, must be cost-effective, manufactured for large-scale production, conveniently sterilised, and also must have appropriate storage requirements and stability.[77] Allograft fulfils those conditions. On the other hand it has also been claimed that allograft can provoke disease transmission and immunogenicity.[49] Nevertheless, despite the large number of allografts used, there appears to be no overt risk of infection associated with the use of allograft bone in spinal surgery.[25,59] Combination of allograft with new BMPs in the form of cancellous or tricortical form is theoretically a good strategy which has not been well studied.

Demineralised bone matrix (DBM) is allogeneic bone that has been decalcified, losing most of the mineralised component but retaining type-I collagen, the non-collagenous proteins, and transforming growth factors (TGFs), including BMPs.[42,87] Most of the literature concerning the bone healing power of DBM has been carried out in cell cultures in vitro or animal models in vivo. The efficacy of DBM in humans has not been proven.

BMPs

BMPs can initiate the cascade of bone formation, including the migration and differentiation of pluripotent MSCs into pro-osteoblasts. Currently, two BMPs (BMP-7 and BMP-2) are commercially available and have been evaluated in a variety of clinical situations, including spinal fusion.[2,9,22–24,35,39,43,54,55,60,87,88,95] Although most studies have generated encouraging data, large well-designed, controlled clinical trials for each BMP and for each anticipated application need to be performed, not only to define the clinical efficacy but also to clearly define safety parameters for these highly osteoinductive compounds.

According to literature data, results of BMPs for spinal arthrodesis are similar to those of autograft in animals[16,57] and also in humans.[22] In animal models it has been shown that BMPs can also be added as expanders in autograft during spine fusion.[54,72,73] The American Food and Drug Administration (FDA) has been very restrictive in their approval of BMPs for human use.[30] However, since the incidence of spinal arthrodesis non-union can be up to 35%,[51,83] the FDA and also European National Agencies have made room for humanitarian use, "off-label", of BMPs in spinal primary and revision surgery. Currently, there have been many studies on the effectiveness of BMPs for cervical spine fusion[4] and particularly lumbar fusion either for posterolateral[22,23,43,88] or for interbody[55,60,80,91] arthrodesis. However, a recent meta-analysis of randomised controlled clinical trials carried out in order to evaluate the radiographic and clinical effectiveness of iliac crest autograft and BMPs within the context of posterolateral fusion of the lumbar spine, found that although the radiographic results appeared better in the BMP group, the exact role of the type, dose and carrier of BMPs and the cost-effectiveness of their use need further clinical delineation.[65] In addition, although the use of BMPs for thoracic and lumbar surgery appears safe,[22] its use in cervical surgery seems inadvisable as neck swelling afterwards may provoke severe dysphagia and even respiratory problems.[10,14,95,96] The risk of heterotopic ossification leading to spinal or foraminal stenosis when BMPs are used once the spinal canal has been opened has not been documented.[57] Recent database studies on off-label indications have shown that in the 92.8% of 340,251 cases in which BMPs were used for spinal surgery, dispersion of variables such as anterior or posterior approaches, primary or revision surgeries, cervical or lumbar techniques, use of interbody devices, and disparities in BMP used, makes it very difficult to draw conclusions.[63]

Calcium phosphate compounds

Calcium phosphate biomaterials have shown their qualitative efficiency as bioresorbable and osteoconductive synthetic bone graft substitutes in animal and clinical studies, in combination with bone marrow aspirate or as an extender for autologous bone graft, achieving level I clinical evidence.[18,19,27,28,29,37,97–103] Focus of the clinical research has been β-TCP based products. A recent development is the combination of β-TCP products with collagen for improving handling and osteopromotive effects. Calcium sulphate has evidence level II as a bone expander for spinal fusion.[8] Synthetic hydroxyapatite/collagen (HA/collagen) is also characterized by high osteoconduction and osteopromotion and provides an environment for cell migration from host bone tissue.[64] The application of HA/collagen in combination with bone marrow [85] or growth factors [82] has been well investigated. Anyhow, as bone cells are needed and calcium phosphate compounds have no osteogenic or osteoinductive properties, clinical outcomes must be studied under adequate randomized clinical trial designs.

Cages

Cages are metallic structures – usually titanium made – used for spinal interbody fusion promotion. Cages have strong mechanical support, and are friendly to osteoprogenitor cell proliferation. The idea of using cages is to avoid the morbidity of tricortical harvesting, and also its resorption phase which results in reduction of its strength for vertical support. Interbody cages provide a wonderful early support to compression forces exerted by the vertebrae above and below. However, secondary mobilisation rates, stress shielding, and ensuing failure are its most common complications. Since cages are not live material, have stiffness different to that of bone, and have a very long distance of vascularisation to autograft introduced in its compartments, according to recent reports, cages appear not to have solved interbody spinal osteosynthesis in spinal fracture treatment, in degenerative spine stabilisation, or after deformity corrections.[1,44,47,70,78,81,84]

Main variables for outcome evaluation

Age, length of fusion, location, concurrent diseases, and some other variables are definitive for fusion outcome; hence papers on spinal arthrodesis should stratify by these variables at least.

Age is an important factor for MSC population, as in aged people MSC population is inferior to that in younger persons.[12] Since MSCs reproduce themselves in order to achieve a higher population of osteoblasts, smaller MSC populations will result in poorer osteoblast amounts for bone production. Therefore it is to be expected that in older patients spinal fusion has a poorer outcome; consequently more autograft should be added in the elderly in order to supply more MSCs. However, in older people autograft harvesting is more difficult and also more liable to have complications. Hence the stimulation of MSCs contained in autografts by BMPs could be an interesting strategy if successful arthrodesis is to be achieved. Since only BMPs have the bone cell

stimulating role, in these cases BMPs used as expander for autograft could have an important function. Nevertheless a longer spinal segment for arthrodesis in older patients is a challenge and needs alternatives to autograft. In these cases allograft with BMPs could be an option.

Location of arthrodesis and number of segments to be fused are also very important. Usually lumbosacral graft compaction between the fifth transverse process and sacral lateral masses requires a greater amount of graft and has a less favourable biomechanical situation than thoracolumbar arthrodesis. Likewise longer fusions will require more graft and more stimulation factors. Since simple cervical or thoracolumbar fractures will only require instrumentation of three vertebral bodies with two interbody spaces, autograft in young people may be the choice, whereas alternatives, as said before, must be found for older patients or longer segments.

Special cases – such as those fractures in patients with spondylitis ankylopoietica or osteoporosis – will require longer instrumentation for neutralisation purposes, and therefore addition of more bone graft.[52,74] These cases will also require similar alternatives to autograft (Figs. 2 and 3).

New papers with larger samples, better design, and diagnostic tools with optimal predictive value could bring a more accurate light to bear on what should be used for successful spinal arthrodesis and when.[63] In any case it appears that an appropriate combination of biomechanics with biology will always have an overwhelming importance.

Conflict of interest statement

The authors declare that there are no conflicts of interest or any funding source in the study. None of the authors have received any royalties regarding this manuscript.

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