

REVIEW ARTICLE

Advances in Spinal Interbody Cages

Sukrit Jain, BS¹, Adam E M Eltorai, MS², Roy Ruttiman, MS², Alan H Daniels, MD³¹Brown University, ²Warren Alpert Medical School and ³Division of Spine Surgery, Department of Orthopaedic Surgery, Warren Alpert Medical School, Providence, Rhode Island, USA

Since the late 1980s, spinal interbody cages (ICs) have been used to aid bone fusion in a variety of spinal disorders. Utilized to restore intervertebral height, enable bone graft containment for arthrodesis, and restore anterior column biomechanical stability, ICs have since evolved to become a highly successful means of achieving fusion, being associated with less postoperative pain, shorter hospital stay, fewer complications and higher rates of fusion when than bone graft only spinal fusion. IC design and materials have changed considerably over the past two decades. The threaded titanium-alloy cylindrical screw cages, typically filled with autologous bone graft, of the mid-1990s achieved greater fusion rates than bone grafts and non-threaded cages. Threaded screw cages, however, were soon found to be less stable in extension and flexion; additionally, they had a high incidence of cage subsidence. As of the early 2000s, non-threaded box-shaped titanium or polyether ether ketone IC designs have become increasingly more common. This modern design continues to achieve greater cage stability in flexion, axial rotation and bending. However, cage stability and subsidence, bone fusion rates and surgical complications still require optimization. Thus, this review provides an update of recent research findings relevant to ICs over the past 3 years, highlighting trends in optimization of cage design, materials, alternatives to bone grafts, and coatings that may enhance fusion.

Key words: Cage subsidence; Interbody cage; Spine surgery

Introduction

Spinal fusion has been employed to treat a variety of spinal disorders, including degenerative disc disease, spondylolisthesis, trauma, tumor reconstruction and scoliosis for decades¹. Initially, spinal fusion procedures involved liberal autologous bone grafting and muscle dissection with uninstrumented fusion. These procedures were commonly associated with intra- and/or post-operative complications, vertebral non-union (pseudarthrosis) and prolonged recovery. Anterior and posterior spinal instrumentation were later introduced to aid fusion by enhancing spinal stability; these techniques allowed surgeons to realign the spine when necessary^{2,3}. Although spinal instrumentation helped usher in the modern era of spine surgery, spinal fusions continued to frequently be complicated by instrumentation failure, kyphosis, and pseudarthrosis.

In 1988, Bagby proposed using a hollow, porous, stainless-steel interbody cage to treat spondylotic cervical myelopathy in horses⁴. This cage fusion technology was soon adapted for human use, receiving Food and Drug Administration approval for certain spinal disorders in 1996. Interbody cages have since evolved to become a

highly successful means of achieving fusion, being associated with less postoperative pain, shorter hospital stay, fewer complications and higher rates of fusion than bone graft only spinal fusion⁵.

Interbody cage design and materials have changed considerably over the past two decades. The threaded titanium-alloy cylindrical screw cages, typically filled with autologous bone graft, of the mid-1990s achieved greater fusion rates than bone grafts and non-threaded cages. Threaded screw cages, however, were soon found to be less stable in extension and flexion; additionally, they had a high incidence of cage subsidence. From the early 2000s, non-threaded box-shaped titanium (Ti) or polyether ether ketone (PEEK) interbody cage (IC) designs have become increasingly more common. This modern design continues to achieve greater cage stability in flexion, axial rotation and bending⁶.

Cage stability and subsidence; bone fusion rates and surgical complications still require optimization. The purpose of this update is to review reports on topics related to ICs that have been published over the past 3 years (2013–2015). We utilized the key word “interbody cage” to query the PubMed database of the USA National Library of Medicine.

Address for correspondence Alan H. Daniels, MD, Division of Spine Surgery, Department of Orthopaedics, Warren Alpert Medical School of Brown University, 100 Butler Drive, Providence, RI, USA 02906 Tel: 001-401-3301420; Fax: 001-401-3301495; Email: aeltorai@gmail.com

Disclosure: No funding was received for this work.

Received 5 May 2016; accepted 18 May 2016

From the resulting list, we reviewed 262 papers published in either clinical spine surgery or biomedical engineering journals and reporting optimization of interbody cage (IC) design, material, coatings and alternatives to bone grafts. We also evaluated related commentaries (Fig. 1). We categorized, summarized, and reviewed these studies to provide an update of recent research findings.

Cage Design

Porosity

Osteoconductivity has long been an issue with IC technology. With the aim of making cages more osteoconductive, many of the latest cages have been modified to have pores. For example, Yamada *et al.* created a new titanium sheet with a high porosity that is created by a network of interconnecting micro- and macro-pores (Fig. 2)⁷. The sheet also has a triple pore structure that imitates trabecular bone⁷. Using sheep as a model, these researchers compared highly porous titanium sheet cages (without bone graft) with conventional, non-porous Ti alloy cages with autogenous bone graft. They found that their newly designed Ti sheet cages equaled any conventional cage design in terms of bone apposition and

bone growth ratio. Despite bone growth being significantly greater in controls than in patients with titanium sheet cages at 2 months, there was no significant difference at 4 months⁷. Titanium sheet cages take longer to achieve the same degree of stability than conventional cages with autologous graft, suggesting that this new cage design requires bone graft to achieve interbody fusion. Future research should incorporate longer follow-up and assessment of performance in humans to determine whether cages constructed of these sheets are clinically superior⁷.

Number of Screws

Approaching cage design from a different perspective, Reis *et al.* studied whether the number of screws on a cage influences its efficacy⁸. These authors compared a newly designed two-screw anchored cage, a four-screw anchored cage and a four-screw standard plate and cage (Fig. 3)⁸. They found that two-screw anchored cages achieved a significantly greater range of motion than four-screw cages, whereas four-screw cages provided greater stability. Four-screw anchored cages did not differ significantly in performance from the standard plate and cage model.

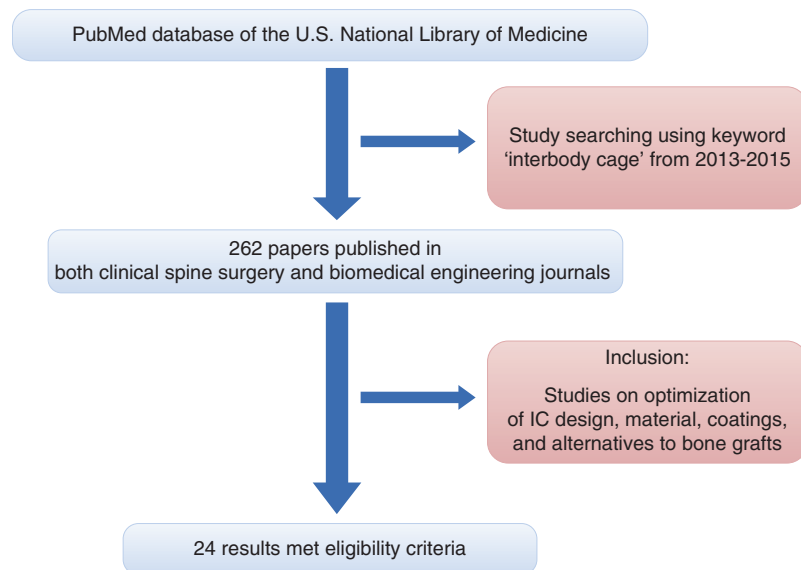


Fig. 1 Flow chart of search of published reports.

Fig. 2 Scanning electron microscopy photographs of a porous titanium sheet at lower magnification (A) and higher magnification (B). The high porosity is created by a network of interconnecting micro and macropores. The sheet also has a triple pore structure (asterisks) that imitates trabecular bone.

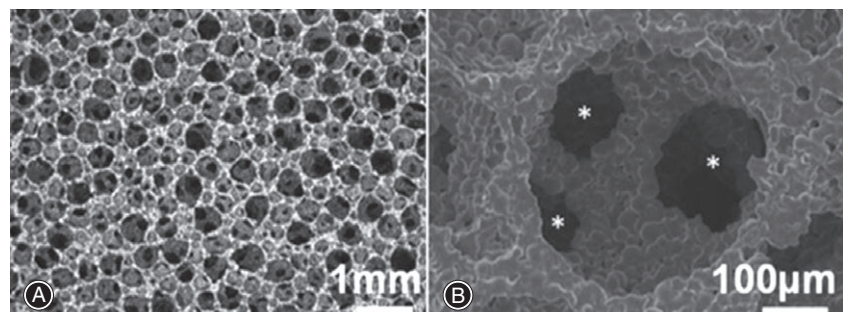




Fig. 3 A representation of a two-screw anchored cage⁸. Investigators have found that two-screw anchored cages result in a significantly greater range of motion than four-screw cages, whereas four-screw cages provide greater stability.

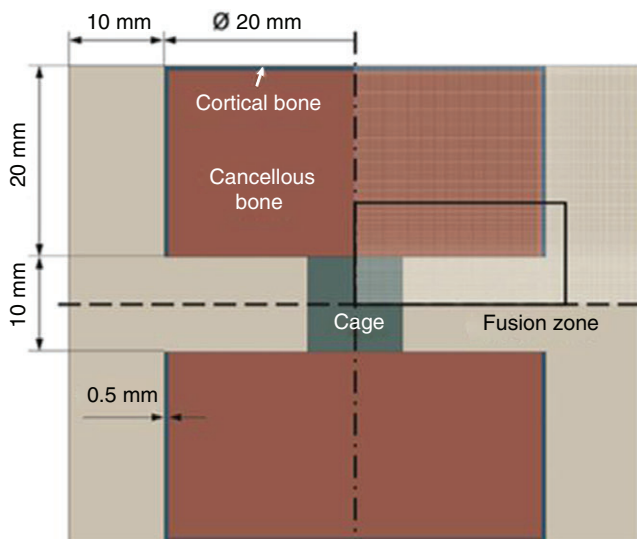


Fig. 4 Representation of the finite element model used to determine which factors should be considered when creating the optimal cage design for lumbar fusion⁹. Investigators found that a compliant cage that allows for strong immediate bone growth hinders future bone formation.

Theoretical Model

Bashkuev *et al.* reported a theoretical model for optimizing cage design. Acknowledging the fact that use of the correct fixation device can minimize fracture-healing time, these authors designed a finite element model to determine which factors should be considered when creating the optimal cage design for lumbar fusion (Fig. 4)⁹. They found that a compliant cage that allows for strong immediate bone growth hinders future bone formation. Thus, the ideal cage creates an environment that allows for bone growth throughout the entire fusion process⁹. Of course, in this complex study, the researchers simplified several factors the authors, including studying specific loading conditions that did not encompass all daily activities⁹. Nevertheless, their findings identified theoretical qualities to attempt to integrate when designing the next generation of cages.

Cage Materials

Titanium versus PEEK

The two main materials currently utilized in interbody cages are Ti and PEEK; which one is superior remains debatable. First utilized in spinal fusion in the 1990s, Ti cages provide a

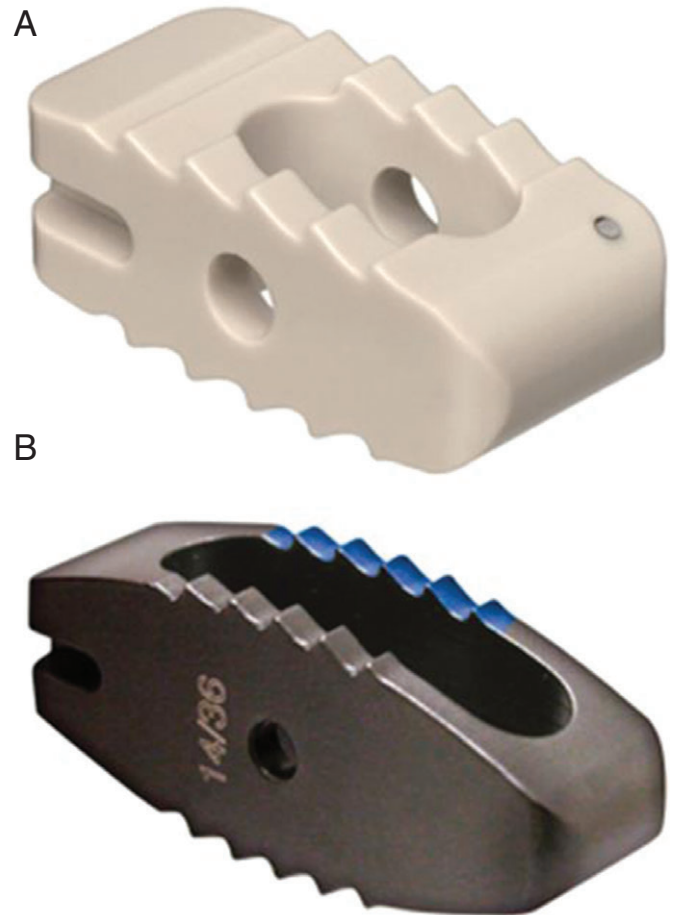


Fig. 5 (A) PEEK cage; (B) Titanium cage¹³.

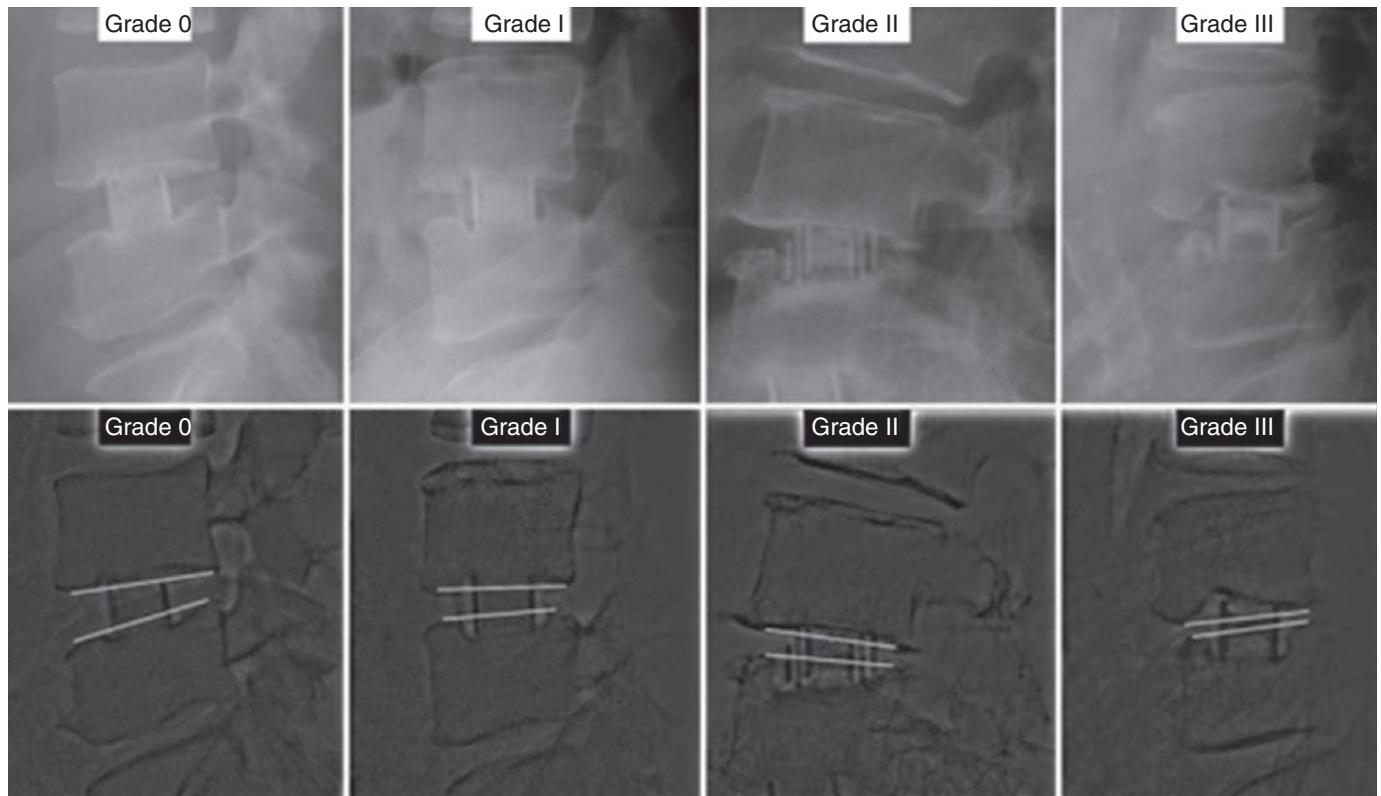


Fig. 6 Radiographic grading of subsidence: Grade III is the most severe¹⁵.

low density, corrosion-resistant scaffolding for vertebral fusion¹⁰. Additionally, the surface of Ti cages can be modified to assist in osteointegration and bone adhesion^{10,11}. Introduced a decade later, PEEK cages are radiolucent, bioinert, MRI compatible and display an elastic modulus that approximates that of bone¹². Studies comparing the performance of PEEK and Ti cages have had mixed results¹¹ (Fig. 5).

Research groups Lingutla *et al.* and Chen *et al.* independently compared Ti and PEEK cages and reported differing results concerning the initial restoration of disc height. Lingutla *et al.* found no difference in disc height between Ti and PEEK cages, whereas Chen *et al.* reported better disc height restoration and long-term clinical outcomes with PEEK cages^{11,14}. However, both studies identified greater subsidence with Ti implants (Fig. 6). Additionally, Chen *et al.* reported inferior clinical outcomes for Ti cages, possibly linked with their tendency to subside¹¹.

Although multiple studies have shown that PEEK achieves better fusion rates and less subsidence than Ti and may thus be the preferred cage material, over-distraction and problems with end-plate preparation continue to compromise the efficacy of PEEK for spinal fusion¹⁶.

Silicon Nitride

Ceramic implants, specifically silicon nitride, are being considered as new cage materials. Kersten *et al.* have submitted

a study protocol outlining a double blind multi-center randomized controlled trial of silicon nitride versus PEEK cages in transforaminal lumbar interbody fusion in patients with degenerative lumbar disc disorders (Fig. 7). The authors consider silicon nitride a biocompatible and osteoconductive material that may be superior for spinal fusion than PEEK, the latter being associated with suboptimal osteointegration and subsequent implant migration¹.

Bioabsorbable

Bioabsorbable cages are currently being explored as an implant option. Daentzer *et al.* compared a bio-absorbable magnesium-polymer cages to bone graft in an ovine model (Fig. 8) and found that even though stiffness increases with time with bio-absorbable cages, bone grafts provide a higher fusion rate¹⁸. A major issue with magnesium-polymer cages is that they do not encourage osteointegration. Future research in this area should aim to find a material that degrades with time, encourages osseointegration and has an elastic modulus similar to that of bone⁸.

Alternatives to Bone Graft

Interbody cages usually require filler material inside them to promote bone growth. Yan *et al.* evaluated beta-tricalcium phosphate as a synthetic bone substitute and found that it generally provides positive spinal stability and



Fig. 7 A composite silicon nitride cervical implant (photograph courtesy of Amedica Corporation, Salt Lake City, UT, USA)¹⁷.



Fig. 8 A skeleton of a magnesium-polymer cage¹⁹.

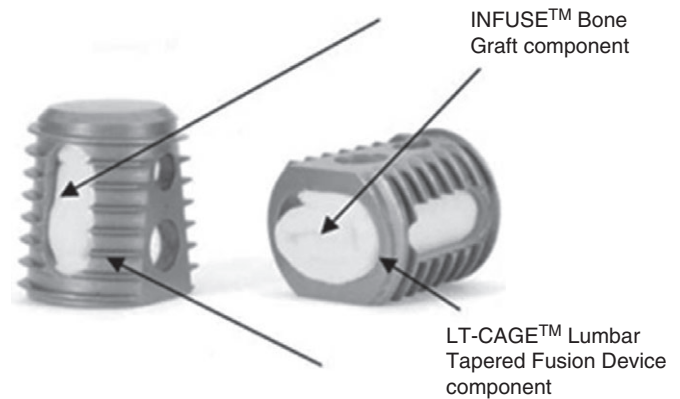


Fig. 10 INFUSE bone graft, which accompanies the LT-CAGE Lumbar Fusion Device and contains bone morphogenic protein 2 (Medtronic Sofamor Danek, Memphis, TE, USA)²³.

fusion (Fig. 9)²¹. While subsidence does occur during the first 6 months, stable fusion begins to be established after the sixth month²¹.

Bone morphogenic proteins (BMPs), cytokines that encourage bone growth by causing differentiation of stem cells into osteoprogenitor cells²², offer another route. The only BMP approved for use in humans BMP-2, because the other feasible BMPs have been shown either to be inferior or not yet superior to autografts (Fig. 10)²². Current research in this field has centered on assessing the viability of BMP-14 and the efficacy of BMPs in other procedures. Animal studies of BMP-14 have shown significant success and clinical research, while still under way, has provided some promising results²². Bone marrow aspirates are another potential option, having been shown to increase fusion without increasing morbidity²².

Enhanced Coatings

Several interbody cages now have additional surface coatings to enhance the bone-cage interface. Gu *et al.* examined the effects of hydroxyapatite (HA) coating and a combination of transforming growth factor beta 1 (TGF- β 1) and insulin-like growth factor-1 (IGF-1) coatings on cage efficacy (Fig. 11)²⁵. In normal physiology, HA crystallizes collagen fibers to make bone matrix, whereas TGF-B1 and

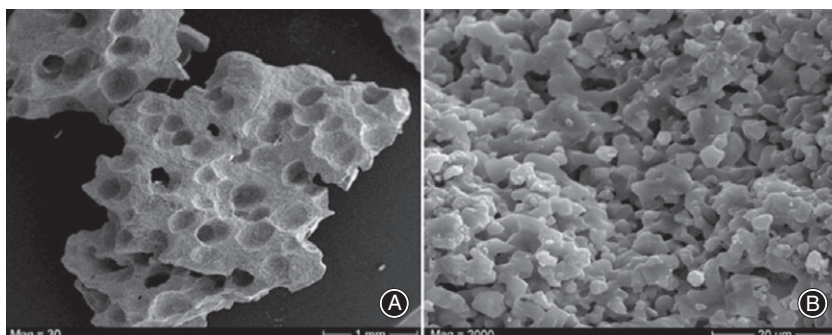


Fig. 9 A beta tricalcium phosphate particle (A: $\times 30$ magnification; B: $\times 2000$ magnification)²⁰.

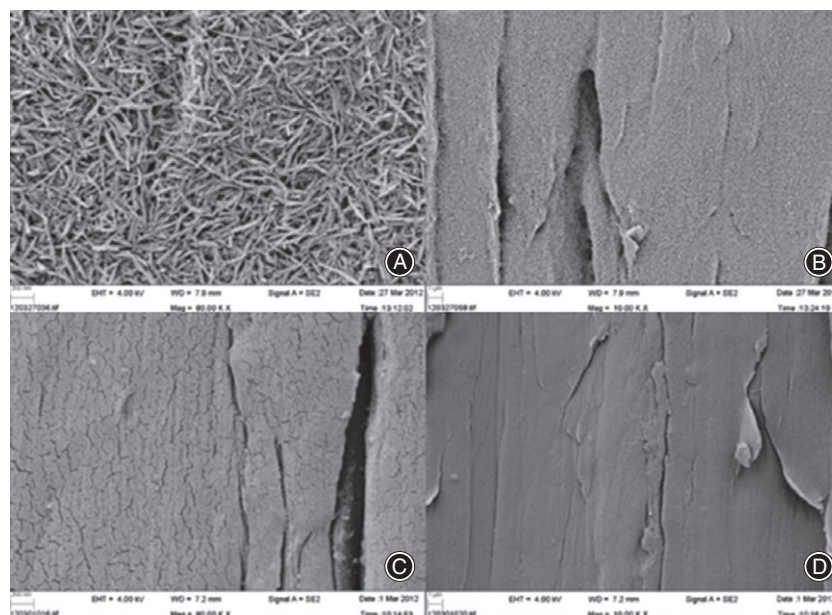


Fig. 11 Scanning electron microscope images of (A) PEEK with HA coating at 80,000 magnification, (B) PEEK with hydroxyapatite coating at 10,000 magnification, (C) uncoated PEEK at 80,000 magnification, (D) uncoated PEEK at 10,000 magnification²⁴.

IGF-1 stimulate replication of osteoblasts, thus ultimately leading to creation of bone matrix²⁵. These researchers compared the effects of a cage on its own, a cage + HA and a cage + HA + TGF-B1/IGF-1 on spine fusion in goats and found that an HA coating increased the number of fibroblasts surrounding the cage and in turn, significantly decreased spine flexion and extension, when compared with a cage alone²⁵. The HA + TGF-B1/IGF-1 combination led to significantly less extension than a cage + HA, suggesting that the addition of TGF-B1/IGF-1 may further reduce range of motion²⁵. Moreover, TGF-B1/IGF-1 can have dose-dependent side effects, such as hypoglycemia and electrolyte shifts. Further investigation of the safety of TGF-B1/IGF-1 coatings in humans is needed²⁵.

Conclusions

Over the past 3 years alone, there have been several developments in cage technology. Advances in cage

design and material have been directed towards improving fusion rates after interbody fusion that displays in humans and animals and decreased subsidence or device migration, all without the need for autogenous bone graft. Some experimental and clinically available cages have demonstrated some of these features; however, a fully optimized cage has yet to be developed.

In such a fast moving field, the latest cage models may become outdated by the time researchers have completely assessed their efficacy. Moreover, difficulties may arise when a certain cage design and material has previously been identified as the superior, first-line option.

Given the nuances and breadth of spinal surgery, one type of cage may be the preferred option for one spine segment or procedure but unsuitable or suboptimal in other situations. Continued research on and innovations in cage design, material, bone graft alternatives and coating will assist surgeons to determine the ideal interbody cage for each patient.

References

1. Kersten RF, van Gaalen SM, Arts MP, et al. The SNAP trial: a double blind multi-center randomized controlled trial of a silicon nitride versus a PEEK cage in transforaminal lumbar interbody fusion in patients with symptomatic degenerative lumbar disc disorders: study protocol. *BMC Musculoskelet Disord*, 2014, 15: 1.
2. Hall JE. Dwyer instrumentation in anterior fusion of the spine. *J Bone Joint Surg Am*, 1981, 63: 1188–1190.
3. Harrington PR, Dickson JH. Spinal instrumentation in the treatment of severe progressive spondylolisthesis. *Clin Orthop Relat Res*, 1976, 117: 157–163.
4. Bagby GW. Arthrodesis by the distraction-compression method using a stainless steel implant. *Orthopedics*, 1988, 11: 931–934.
5. Dimar JR, Glassman SD, Burkus KJ, Carreon LY. Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenetic protein-2/compression resistant matrix versus iliac crest bone graft. *Spine (Phila Pa 1976)*, 2006, 31: 2534–2539.
6. Chong E, Pelletier MH, Mobbs RJ, Walsh WR. The design evolution of interbody cages in anterior cervical discectomy and fusion: a systematic review. *BMC Musculoskelet Disord*, 2015, 16: 99.
7. Yamada K, Ito M, Akazawa T, Murata M, Yamamoto T, Iwasaki N. A preclinical large animal study on a novel intervertebral fusion cage covered with high porosity titanium sheets with a triple pore structure used for spinal fusion. *Eur Spine J*, 2015, 24: 2530–2537.
8. Reis MT, Reyes PM, Crawford NR. Biomechanical assessment of anchored cervical interbody cages: comparison of 2-screw and 4-screw designs. *Neurosurgery*, 2014, 10: 412–417.
9. Bashkuev M, Checa S, Postigo S, Duda G, Schmidt H. Computational analyses of different intervertebral cages for lumbar spinal fusion. *J Biomech*, 2015, 48: 3274–3282.
10. Alvarez K, Nakajima H. Metallic scaffolds for bone regeneration. *Materials*, 2009, 2: 790–832.
11. Chen Y, Wang X, Lu X, et al. Comparison of titanium and polyetheretherketone (PEEK) cages in the surgical treatment of multilevel cervical spondylotic myelopathy: a prospective, randomized, control study with over 7-year follow-up. *Eur Spine J*, 2013, 22: 1539–1546.
12. Orief T, Ramadan I, Seddik Z, Kamal M, Rahmany M, Takayasu M. Comparative evaluation of bone-filled polymethylmethacrylate implant, autograft

fusion, and polyetheretherketone cervical cage fusion for the treatment of single-level cervical disc disease. *Asian J Neurosurg*, 2010, 5: 46–56.

13. Nemoto O, Asazuma T, Yato Y, Imabayashi H, Yasuoka H, Fujikawa A. Comparison of fusion rates following transforaminal lumbar interbody fusion using polyetheretherketone cages or titanium cages with transpedicular instrumentation. *Eur Spine J*, 2014, 23: 2150–2155.

14. Lingutla K, Gudipati S, Pollock R, Davies P, Chopra I, Ahuja S. Radiological outcomes of Peek vs Titanium transforaminal lumbar interbody cages. *Spine J*, 2015, 15: S53.

15. Marchi L, Abdala N, Oliveira L, Amaral R, Coutinho E, Pimenta L. Radiographic and clinical evaluation of cage subsidence after stand-alone lateral interbody fusion: clinical article. *J Neurosurg Spine*, 2013, 19: 110–118.

16. Kim CH, Chung CK, Jahng TA, Park SB, Sohn S, Lee S. Segmental kyphosis after cervical interbody fusion with stand-alone polyetheretherketone (PEEK) cages: a comparative study on 2 different PEEK cages. *J Spinal Disord Tech*, 2015, 28: E17–E24.

17. Arts MP, Wolfs JF, Corbin TP. The CASCADE trial: effectiveness of ceramic versus PEEK cages for anterior cervical discectomy with interbody fusion; protocol of a blinded randomized controlled trial. *BMC Musculoskelet Disord*, 2013, 14: 244.

18. Daentzer D, Willbold E, Kalla K, *et al.* Bioabsorbable interbody magnesium-polymer cage: degradation kinetics, biomechanical stiffness, and histological findings from an ovine cervical spine fusion model. *Spine (Phila Pa 1976)*, 2014, 39: E1220–E1227.

19. Daentzer D, Floerkemeier T, Bartsch I, *et al.* Preliminary results in anterior cervical discectomy and fusion with an experimental bioabsorbable cage – clinical and radiological findings in an ovine animal model. *SpringerPlus*, 2013, 29: 1–8.

20. Vivorte. *Kentucky: Trab-X SB™ synthetic bone matrix: beta tricalcium phosphate granules*. 2016. Available from: <http://www.vivorte.com/index.php/products/trab-x-sb-bone-matrix> (accessed 17 April 2016).

21. Yan JL, Chen JF, Lee ST, Chang CN, Liao CC. Surgical outcomes of Cervios chronos cage implantation for degenerative cervical intervertebral disk disorder. *Neurosurg Quart*, 2014, 24: 161–166.

22. Hustedt JW, Blizzard DJ. The controversy surrounding bone morphogenetic proteins in the spine: a review of current research. *Yale J Biol Med*, 2014, 87: 549.

23. Food and Drug Administration. *InfUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device - P000058*. USA Food and Drug Administration, 2013. Available from: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm083423.htm>

24. Johansson P, Jimbo R, Kjellin P, Currie FF, Chrcanovic BR, Wennerberg A. Biomechanical evaluation and surface characterization of a nano-modified surface on PEEK implants: a study in the rabbit tibia. *Int J Nanomedicine*, 2014, 9: 3903–3911.

25. Gu Y, Zhang F, Lineaweaver WC, *et al.* *In vivo* study of hydroxyapatite-coated hat type cervical intervertebral fusion cage combined with IGF-I and TGF-β1 in the goat model. *Clin Spine Surg*, 2016, 29: E267–E275.