REVIEW ARTICLE

Evolution of Design of Interbody Cages for Anterior Lumbar Interbody Fusion

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Anterior lumbar interbody fusion (ALIF) is one of the surgical procedures for the relief of chronic back pain, radiculopathy and neurogenic claudication in patients with degenerative lumbar spine disease that is refractory to conservative therapy, low-grade spondylolisthesis and pseudo arthrosis. Over the past half century, both the surgical techniques and instrumentation required for ALIF have changed significantly. In particular, the designs of ALIF cage and the materials used have evolved dramatically, the common goal being to improve fusion rates and optimize clinical outcomes. The increasing popularity of ALIF is reflected by the increasing abundance of published studies reporting clinical outcomes, surgical techniques and grafting options for ALIF. Developments in cage designs include cylindrical *Bagby and Kuslich*, cylindrical ray, cylindrical mesh, lumbar-tapered, polyethyl-etherketone cage and integral fixation cages. Biologic implants include bone dowels and femoral ring allografts. Methods for optimization of cage design have included cage dimensions, use of novel composite cage materials and integral fixation technologies. However, the historical development and evolution of cages used for ALIF has not been extensively documented. This article therefore aims to provide an overview of the historical basis for the anterior approach, evolution in design of ALIF cage implants and potential future research directions.

Key words: ALIF; Anterior lumbar interbody fusion; Cage; Design; Review of published reports

Introduction

For patients with degenerative lumbar spine disease refractory to conservative treatment, anterior lumbar interbody fusion (ALIF) is one of the potential surgical procedures for the relief of chronic back pain, radiculopathy and neurogenic claudication[1,2]. There is a limited but increasing amount of evidence for the safety and efficacy of the anterior interbody fusion approach compared with posterior approaches[3]. In 1932, Capener was the first to describe the use of an anterior approach for treatment of spondylolisthesis[4]. Since this initial study, ALIF has evolved to become an effective surgical option for various lumbar degenerative pathologies, including degenerative disc disease (Fig. 1), low-grade spondylolisthesis and pseudoarthrosis[5].

The ALIF procedure involves retraction of the great vessels in the retroperitoneal region to allow ventral access to the spinal structures, followed by discectomy and cage implantation. ALIF offers the potential advantages of facilitating normal lumbar lordosis, indirect enlargement of neural foramina space and increased intervertebral height, whilst reducing the risk of damaging posterior paraspinal muscles and neural structures[6–9]. Furthermore, the anterior approach also allows implantation of larger bone cages and grafts, facilitating improved initial stability and compression of the fusion construct[10–14]. Some studies have reported that ALIF may be associated with reduced blood loss, shorter operative duration and reduced blood transfusion requirements than other approaches[15]. However, the ALIF procedure is also associated with risks of injury to major vasculature, intestinal and urethral damage, and injury to the hypogastric nerve plexus leading to retrograde ejaculation[16–18].

Over the past half century, both the surgical techniques and instrumentation required for ALIF have changed significantly. In particular, the designs and materials of ALIF cages have evolved dramatically, the common goal being to improve fusion rates and optimize clinical outcomes. The increasing popularity of ALIF is reflected by the increasing abundance of published studies reporting clinical outcomes, surgical techniques and grafting options for ALIF[3,6,10,12,15,19–24]. In recent years, development of lumbar

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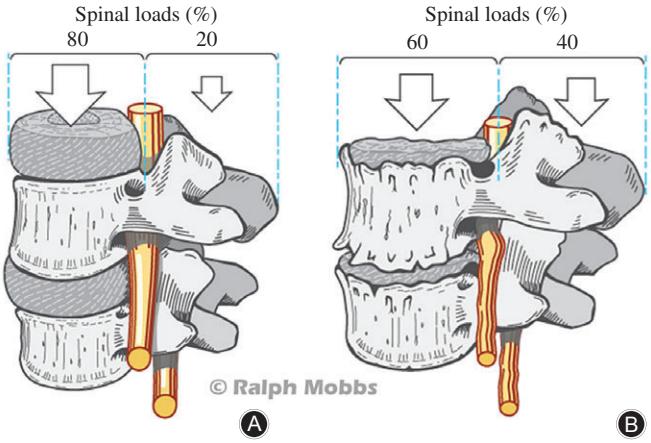

Fig. 1 Degenerative disc disease as a rationale for ALIF. (A) Distribution of spinal loads on the anterior and posterior weight-bearing columns in a normal lumbar spine. (B) Shifting of spinal loads to the posterior column as a result of degenerative pathology in the lumbar spine.

fusion surgery has focused on reduction of surgical trauma by using minimally invasive approaches, new graft materials and cage designs[25]. However, the historical development and evolution of cages used for ALIF has not been extensively documented. This article therefore aims to overview the historical basis for the anterior approach, evolution in the design of ALIF cages and potential future research directions.

Methods

A review of published reports concerning the evolution of cage designs for ALIF was performed. In accordance with international guidelines and recommendations, an electronic search the Medline/Pubmed database from inception to February 2015 was performed using the following key words and MeSH terms: "ALIF", "anterior lumbar interbody", "fusion", "cage", "implant" and "design[26–28]". Inclusion criteria included studies focusing on the design, methodology or outcomes of the ALIF approach. Studies that focused on other fusion approaches, non-English language studies and non-human studies were excluded. Related articles were also assessed; original articles are cited where possible. The present review includes assessment and overview of 109 articles (Fig. 2).

Development of Anterior Fusion Surgery

Capener first introduced the anterior approach for insertion of a bone graft spacer for treatment of 32 patients with spondylolisthesis in 1932[4]. Although he concluded that the anterior approach was theoretically biomechanically ideal, this view was met with resistance from his peers, Stauffer and Coventry making the criticism that "too much surgical trauma to the patient" was involved[29]. However, shortly thereafter several surgeons reported successful utilization of the anterior approach for spondylolisthesis, including

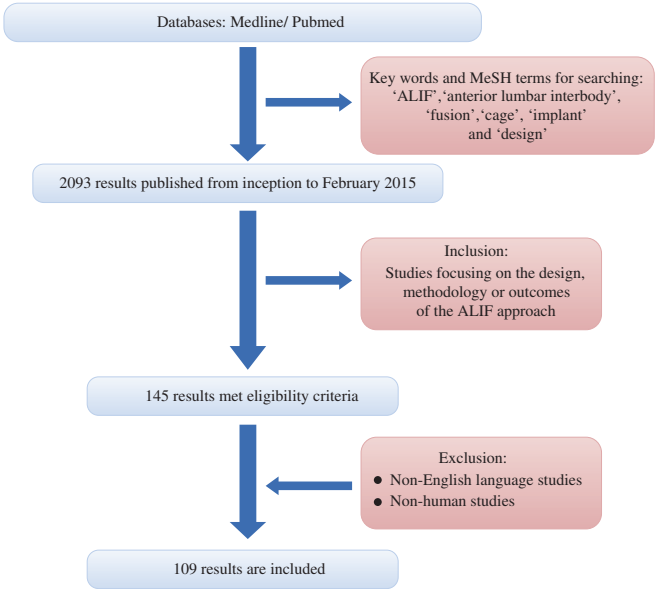

Fig. 2 Flow-chart of search of published reports showing the process of inclusion and exclusion.

Mercer, Friberg, d'Aubigne and Cauchoix[30–32]. In 1944, Iwahara proposed a retroperitoneal technique and soon after, in 1948, Lane and Moore reported the first use of ALIF for the treatment of lumbar degenerative disc disease[33,34]. They used allogenic bone graft in 97 patients and achieved an excellent clinical success rate of 94% and fusion rate of 54%.

Considered by many as the initial foundation for modern era ALIF surgery, Hodgson and Stock employed Iwahara's retroperitoneal technique and different types of graft material to treat Pott disease[35,36]. Their approach involved debridement of necrotic tissue, followed by decompression of the spinal canal and insertion of corticocancellous blocks of autogenous bone. Around the same time, Cloward utilized a similar technique, the difference being use of a cylindrical-shaped corticocancellous dowel[37]. Whilst Cloward used a posterior approach, his use of dowels and his techniques for disc removal and endplate preparation were extensively adopted by surgeons opting for the anterior fusion approach, including Harmon in 1963 and Sacks in 1965[38,39]. O'Brien *et al.* later proposed the use of trapezoid blocks as a modification to prior grafts for treatment of discogenic pain by ALIF[40]. O'Brien *et al.* subsequently developed this into a hybrid approach involving a biologic fusion cage comprising femoral cortical allograft rings packed with autogenous cancellous bone graft (Fig. 3).

Following the above pioneering innovations, there was an increasing use of stand-alone ALIF in the 1970s and 1980s characterized by great variation in surgical techniques and discrepancies between groups concerning ALIF fusion success rates. For example, Lane and Moore reported fusion rates of 54%, Adkins fusion rates of 1% and Harmon fusion rates of up to 95%[34,38,41]. As a consequence, ALIF procedures

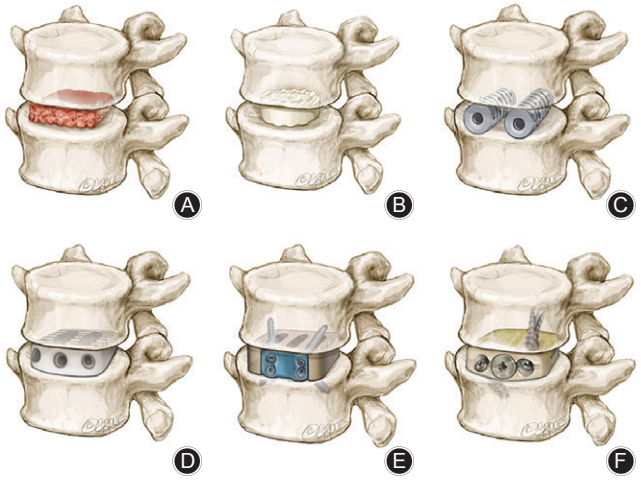

Fig. 3 Evolution of anterior lumbar interbody fusion (ALIF) cage designs. (A) Autograft block; (B) femoral ring allograft; (C) BAK cage; (D) PEEK cage; (E) SynFix implant; (F) Ti-PEEK cage.

supplemented by posterior fusion became increasingly popular. Even in current clinical practice, there is still debate as to whether stand-alone ALIF or posterior supplemented ALIF is the optimal approach for lumbar degenerative spinal disease. However, during this time, there have also been advances in ALIF instrumentation and access techniques, including the introduction of implant cages or devices to improve stabilization and restore disc height.

Cage Design Evolution

Threaded Titanium Cages

Cylindrical BAK Cage

The history of cages used for ALIF stems back to the original cage implant developed by Bagby, an orthopaedic surgeon in Washington, for the treatment of cervical instability and myelopathy due to Wobbler's syndrome in thoroughbred horses[42]. Known as the "Bagby basket", it was the first cage to consist of a stainless steel cylinder and was packed with horse autograft, facilitating successful fusion with good early stability and improved arthrodesis[42–44].

To adapt the Bagby basket for human use, in the late 1980s Kuslich *et al.* introduced several changes to the cage design, including the use of a threaded hollow titanium cylinder with thick perforated walls. This allowed the cage to be screwed onto the endplates of the adjacent vertebrae, thus promoting stabilization and fusion. Furthermore, the hollow cage could be packed with cancellous bone chips, which eliminated the need for autografts[42–45]. At the time, the use of autografts as in the Cloward technique had produced poor results with high mortality and morbidity. This new cage for human use was named the Bagby and Kuslich (BAK) titanium cage (BAK; Spine-Tech, Minneapolis, MI, USA) and was first successfully implanted in humans in 1992 using a posterior approach[46]. Soon after, the use of interbody cages was quickly adapted for an anterior approach for fusion, these being approved by the Food and Drug Administration in 1996.

Cylindrical Ray Cage

Ray further modified the BAK cage, using a design with deeper threads[47]. This promoted "self-tapping" and facilitated stabilization. Furthermore, the Ray cage is reportedly associated with fewer artefacts on imaging studies than BAK cages and can be implanted via a posterior or anterior approach[48].

Cylindrical Mesh Cage

Titanium mesh cages was first developed and introduced in 1986 by Harms and Biederman. Although there have been few reports concerning the use of titanium mesh cages for anterior lumbar fusion, the results published thus far have cited optimistic results[49–51]. The design of these cages involves titanium mesh that has been rolled into a cylindrical shape and reinforced with rings at each end. Titanium mesh cages are traditionally filled with autograft and achieve a high rate of arthrodesis; however, there may be up to 25% complication rates associated with obtaining bone from the iliac crest[52–54]. Recent studies have shown that alternatives to grafts, including coralline hydroxyapatite and demineralized bone matrix, are effective[55].

Lumbar-tapered Cage

Several studies have demonstrated that wider implants are associated with improved segmental stability[20,56,57]. These have higher axial strength to resist subsidence than the narrower area of cylindrical implants. This finding has led to the introduction of lumbar-tapered or trapezoid cages. Specifically, lumbar-tapered cages are wedge-shaped, allowing restoration of the spine to more physiologically correct alignments and angles. These provide similar benefits to the cylindrical cages, however, lumbar-tapered cages allows symmetric reaming of endplates, improving lordosis. These cages can be packed with bone morphogenic protein or autograft.

The use of ALIF for patients with severe discogenic pain for stabilization of vertebral segments has accelerated since the development of these titanium cages[46–48,58–62]. Limitations of threaded cylindrical titanium cages include the use of solid titanium, which prevents accurate radiological assessment of the fusion mass. The stiffness of the titanium cage may also promote its subsidence into adjacent vertebrae, a long-term complication associated with this cage.

Polyetheretherketone (PEEK) Cage Devices

The use of titanium and titanium alloys has proliferated in the spine surgery realm since the 1940s because of its biocompatibility, low density of approximately 4700 kg/m^3, and robust passivation due to TiO_2 formation, which provides impressive resistance to corrosion[63]. However, the use of titanium and its alloys also poses several issues for anterior

lumbar fusion implants. Firstly, there is a mismatch between the elastic modulus of titanium (110 GPa) and that of vertebrae trabecular bone (2.1 GPa) and cortical bone (2.4 GPa[64]). This elastic modulus mismatch results in reduced stress shielding around the implant which, together with local inflammation, can precipitate graft subsidence and bone–graft interface fractures[65–68]. A second major issue with the use of titanium cages and elastic modulus mismatch is that it causes imaging artefacts because of its high radiodensity, and thus hinders accurate assessment of fusion status[69].

To address the above-mentioned disadvantages of titanium and titanium alloys, alternative materials, including PEEK and carbon fiber, were developed. PEEK fusion cages were introduced by AcroMed (Raynham, MA, USA) in the 1990s, and pioneered by polymer engineer McMillin; these implants were known as Brantigan cages[70]. The initial anterior interbody cage devices constructed of PEEK comprised either a hexagonal or round device designed as a spacer with a central cavity for bone graft placement. PEEK offers several advantages: PEEK cages have a modulus of elasticity similar to that of cortical bone, which may promote even load sharing and stress distribution[71,72]. This may translate into lower subsidence rates and potentially higher fusion rates. Furthermore, the use of carbon fiber reinforcement may further reduce any differences in elastic modulus between PEEK and bone, PEEK anterior fusion cages are biocompatible and the radiolucency of PEEK implants permits improved assessment of fusion on imaging[73,74]. Some studies have suggested that PEEK materials are relatively resistant to microbial adhesion and hence associated with lower infection rates than their titanium counterparts[75,76].

Several studies have evaluated anterior lumbar fusion using PEEK cages. In one of the earliest biochemical studies, Schleicher *et al.* demonstrated acceptable flexion and extension loading in a test PEEK cage compared with an established anterior lumbar fusion cage[77]. In a prospective 2-year follow-up study, Hoff *et al.* demonstrated significant improvements in Oswestry Disability Index and Visual Analog Scale scores in 32 patients undergoing ALIF with PEEK cages. Fusion rates were reportedly 93% postoperatively and 70% at final 24-month follow-up. More recently, a study of 40 patients demonstrated solid interbody fusion in 96.4% of them after ALIF using PEEK cages with posterior instrumentation[78].

Integral Fixation Cages

Stand-alone ALIF cages have been developed over the last 15 years and rapidly grown in popularity because of ease of instrumentation and improved biomechanics that eliminate the need for further posterior fixation. In a study by Cain *et al.*, the first stand-alone ALIF implant "Test-device" demonstrated significantly more stability than a traditional anterior cage with translaminar facet screws in flexion and rotation and similar stability to pedicle screw fixation[79]. Stand-alone integral fixation ALIF cages have the potential to reduce complications associated with a combined anterior and posterior instrumentation[77,80,81].

The first integral fixation device on the market that was constructed of PEEK with an integral fixation screw construct was the SynFix (Synthes Bettlach, Solothurn, Switzerland) and gained widespread popularity worldwide because of its excellent biomechanics and ease of use. The SynFix system is a PEEK implant with an integrated anterior plate that additionally stabilizes the motion segment using four angle-locked screws. An early study investigating this cage in stand-alone ALIF demonstrated a 70.6% fusion rate, and 68.7% fusion when posterior instrumentation was added. More recently, an investigation of 32 ALIF procedures performed using the SynFix system with recombinant human bone morphogenetic protein-2 demonstrated solid fusion in 29 patients (90.6%) at 6-month follow-up, similar to values reported for ALIF with posterior instrumentation and bone morphogenetic protein-2[82]. In another recent study of stand-alone ALIF with PEEK, a fusion rate of 96.3% was demonstrated at 12-month follow-up in 65 patients with degenerative lumbar disc disease[83]. These preliminary studies provide promising results for integral fixation cages for stand-alone ALIF; these findings require further confirmation by additional long-term follow-up studies.

Biologic Implants

Bone Dowels

Threaded bone dowels derived from the diaphysis of freeze-dried femurs or tibias have been used as an alternative to titanium cage constructs. Bone dowels are deployed in a similar fashion to traditional titanium cages and involve a dowel holder for impacting the dowel into the appropriate position. Bone dowels offer several advantages, including the transmission of more physiological forces than titanium. Similar construct stiffness and biomechanical stability has been demonstrated for dowel and interbody fusion cage constructs[84,85]. Bone dowels also have a modulus of elasticity similar to that of native bone and would therefore provide better fusion rates than titanium and carbon fiber alternatives. Furthermore, natural bone material is more radiolucent than titanium, thus making fusion with bone dowels easier to assess by imaging intraoperatively. Bone dowels can be used in the presence of infections because they are made of a biological substrate.

Femoral Ring Allografts

Allograft biological cages were developed with the aim of providing mechanical support and stability whilst using biocompatible materials with physiological properties. Femoral ring allografts are biological cages machined from allograft into wedge-shaped rings with "teeth" that can grip onto adjacent vertebrae and improve the stability of the spacer. Given that these spacers have hollow centers, they can be filled with further allograft or bone morphogenic protein to further promote fusion of the biologic cage[86–89].

Cage Design Optimisation

Cage Dimensions

To optimize the design of anterior lumbar fusion implants, pathological changes to spinal anatomy must be considered. The primary consideration of a fusion technique and implant cage is its ability to restore normal anatomy, including foraminal area and volume, disc height, lumbar lordosis and sagittal balance[6–9]. Degenerative changes in the lumbar spine may affect these variables; a commonly quoted change is foraminal narrowing leading to radicular pain and loss of disc height[90,91]. Recently, the pedicle-to-pedicle technique was developed as a standardized radiographic approach for indirectly demonstrating significant improvements in foraminal dimensions and disc height with ALIF using a stand-alone PEEK interbody implant[92]. Foraminal height and area are important variables to consider when designing new ALIF implant and determining whether one design is superior to another[92,93].

Modern ALIF cage designs have a variety of different features and dimensions to ensure maximal clinical and fusion outcomes[3,6,10,12,15,19–24]. Because of differences in initial stability and disc space height between lumbar levels and individuals, ALIF cages are manufactured in a variety of sizes. ALIF cages relieve radicular pain by restoring disc space height, which thus indirectly restores foraminal height and area[92,93]. The architectural design of an implanted ALIF fusion cage has been recognized as a key factor in modulating mechanical dynamics and biological functions in ALIF. However, it must also be recognized that over-distraction can lead to the complications of non-union, postoperative neck pain and poor clinical outcomes resulting from high pressures between graft and lumbar vertebra end plates.

Cage width and length are also important variables for ensuring maximal surface contact and stability of ALIF. Greater implant areas improve transmission of loads to adjacent segments. A further advantage of this is the potential reduction in adjacent level pain[94]. Greater implant area may also facilitate restoration of a lordotic curve, thus creating better physiological stress[95]. Biomechanical studies have demonstrated that covering more than 30% of the endplate area with bone grafts facilitates improved load carrying capacity. However, it must be noted that the optimal dimensions are dictated by lumbar anatomy: an implant that is too small will provide inadequate stability whereas an implant that is too large can damage surrounding structures.

Composite Cage Materials

Although PEEK has favorable mechanical properties, its chemical inertness limits its ability to osseointegrate into the surrounding bone environment. Thus, a myriad of options for cage materials have been developed with the aim of improving PEEK bioactivity, including hydroxyapatite (HA)-PEEK and Ti-PEEK composite cages (Fig. 4).

Given that natural bone consists of fine HA, the natural response would be to develop a composite cage with HA, which would improve bio-integration with its environment. There have been several approaches to integrating HA with PEEK cages. In 1988, HA was added to PEEK in an attempt to create a composite material that would more closely mimic natural bone substance[96]. This concept was recently reintroduced by Wong *et al.*, who developed a strontium-containing HA-PEEK composite with similar bending modulus to cortical bone that enhanced *in vitro* bioactivity[97]. Other recent studies by Khor's group have demonstrated that PEEK with 30% volume HA has an elastic modulus similar to that of human cortical bone[98,99]. Another way to create a HA-PEEK composite is to coat PEEK cages in nanocrystalline HA, which has been shown to be superior to uncoated implants in terms of osseointegration[100].

Another type of composite material currently under investigation is Ti-PEEK. Using a PEEK cage composite with TiO_2 particles manufactured by mixing compression and model, Wu *et al.* demonstrated significantly better osseointegration than with PEEK alone[101]. They reported better cell attachment and spreading than with pure PEEK and better bone regeneration around the composite implant *in vivo*. Similar conclusions have been reported by Han *et al.*, who have also demonstrated that Ti-PEEK composite materials have the promise of improved bioactivity[102].

Other implant materials, including silicon nitride and tantalum, are also under investigation. Nitinol, an alloy consisting of 50% nickel and 50% Ti with shape memory and superelastic properties, is also a potential option for implant material[103–105]. Recent studies have also tested bioabsorbable cages manufactured using poly-L-lactide-co-D, L-lactide. This material absorbs over time without leaving any foreign material in the spinal segment[106]. These

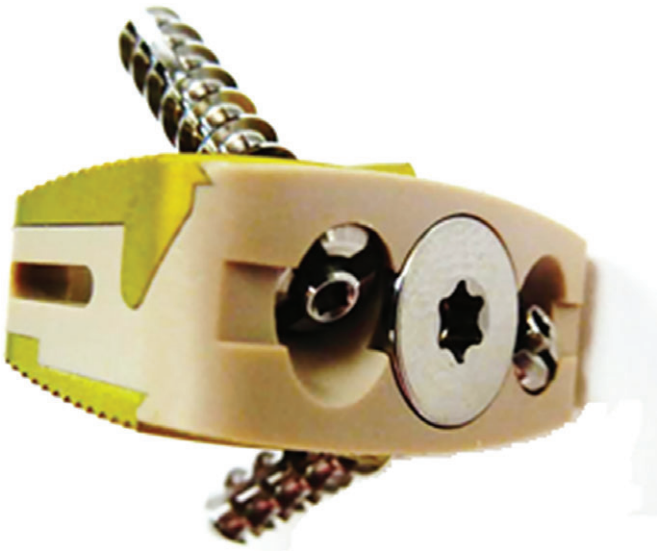

Fig. 4 TI/PEEK composite device for improved osseointegration. Recent developments have seen increasing use of PEEK in vertebral body fusion. More novel approaches to improving PEEK have included the introduction of Ti-PEEK composites and coatings.

Fig. 5 Redmond lumbar cage (A-SPINE Asia). (A) Superior view showing central beveled keel. (B) Lateral view shwoing angulated ridges and composite design and Ti end-plate inlay, fixed in a PEEK body. (C) Anterior view showing two integrated screw fixation.

Fig. 6 Cage with Fin device for improving initial stability. Current developments in cage fixation technology include an implantable fin (ROI-A Oblique; LDR), rotatable teeth and expanding screws (A-Spine ASIA) for fixation.

materials exhibit the necessary rigidity at the time of implantation, then gradually degrade, improving radiological assessment. However, there has been limited experience with this implant material with contradictory results; thus, further studies are warranted[107–111].

Integral Fixation Technologies

Most integral fixation devices use screw technologies to secure the implant to the endplate above and below the device. There are a variety of devices with two, three or four screw designs for assisting initial implant fixation. The design of the fixation method in an integral fixation device may affect the biomechanics of the ALIF cage and must therefore be taken into consideration. Buttermann *et al.* compared three cage types: a PEEK spacer with small ridges, a modular interbody device with end-plate spikes and a dual tapered threaded interbody cage[112]. Cages with end-plate spikes provided better motion segment rigidity in bending modes and particularly in torsion, which may have implications in terms of the design of future ALIF implants[112].

A variety of other devices use additional fixation methods such as an implantable fin (ROI-A Oblique; Zimmer-Biomet, Brognard, France), rotatable teeth and expanding screws (A-Spine ASIA, Taipei, Taiwan) for fixation (Figs 5–6).

Conclusions

Whilst great strides have been made in the development of ALIF cages over the past decade, from bone grafts to composite cages, the ALIF cage continues to evolve into the future. Current efforts are focused on improving bioactivity and osseointegration of ALIF cages and on streamlining anterior fixation with integrated screw cages. Multiple promising new designs are currently in experimentation and testing, however, the inadequate available clinical evidence and lack of comparisons between different models have prevented definitive conclusions regarding the advantages and disadvantages of one implant over another. Future designs will benefit from continued collaborative biomechanical studies, experimentation and clinical studies.

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