Title: Applications of 3D printing in the management of severe spinal conditions

Authors: Elena Provaggi[1], Julian J. H. Leong[1,2], Deepak M. Kalaskar[1]

[1]Centre for Nanotechnolgy & Tissue Engineering, Division of Surgery and Interventional Science, Uiversity College London, London, UK

[2]Royal National Orthopedic Hospital, Stanmore, London, UK

Corresponding author: Dr Deepak M. Kalaskar, Department of Surgery and Interventional Science, UCL Medical School, London, NW3 2QG, UK.

Email: d.kalaskar@ucl.ac.uk

Abstract

The latest and fastest-growing innovation in the medical field has been the advent of three-dimensional (3D) printing technologies, which have recently seen applications in the production of low-cost, patient-specific medical implants. While a wide range of 3D printing systems has been explored in manufacturing anatomical models and devices for the medical setting, their applications are cutting-edge in the field of spinal surgery. This review aims to provide a comprehensive overview and classification of the current applications of 3D printing technologies in spine care. Although 3D printing technology has been widely used for the construction of patient-specific anatomical models of the spine and intraoperative guide templates to provide personalized surgical planning and increase pedicle screw placement accuracy, only few studies have been focus on the manufacturing of spinal implants. Therefore, 3D printed custom-designed intervertebral fusion devices, artificial vertebral bodies and disc substitutes for total disc replacement (TDR), along with tissue engineering strategies focused on scaffold constructs for bone and cartilage regeneration, represent a set of promising applications towards the trend of individualized patient care.

Key words

3D printing, rapid prototyping, spinal surgery, patient-specific, customized spinal implants, intervertebral fusion devices

Introduction

Low back pain caused by degenerative disc diseases, spinal deformities and injuries constitutes a growing problem within the modern society, affecting over 80% of the population worldwide[1]. Total incremental direct health care costs attributable to low back pain in the U.S. were estimated at $26.3

billion in 1998[2], while a more recent economic analysis carried out in the UK has estimated that direct healthcare cost for lower back pain is increasing and currently over £1.6 billion per year[3]. Most of the spinal surgeries are performed to relieve lower back pain, which has been reported to cause loss of mobility and even disability in some patients[4, 5]. In the UK, spinal surgery is the largest single component of expenditure for the management of low back pain[6], with data evincing more than 4036 lumbar spinal fusion surgeries during 2005 within the UK National Health Service[7]. From 2013 to 2014, Hospital Episode Statistics, which records all admissions in the NHS, reported an increased number of 10,900 spinal fusions performed in the UK for neck and lower back pain. Almost 8,000 of these cases required implantation of fusion cages, while 600 were revision cases.

To address the increasing demand and the wide number of possible surgical procedures and approaches, a huge amount of different spinal implants and devices are currently commercially available. The surgical options vary from spinal fusion, which is to date the most performed surgical procedure for the treatment of degenerative disc diseases, and artificial total disc replacement (TDR), which has been performed recently as an alternative to conventional fusion surgeries. However, despite the increasing clinical data, none of the existing procedures have shown to be completely successful and, at the 24 month follow-up, no significant differences in the clinical results have been found[8]. Revision surgeries are often required to address negative post-operative consequences and they are usually associated with even greater perioperative complications than primary procedures, thus predisposing patients to greater costs and utilisation of resources[9].

In this context, three-dimensional (3D) printing technology has the potential to revolutionize the surgical practice in surgery. The benefits of these emerging technologies in medicine are mainly related to the ability to rapidly convert two-dimensional (2D) digital medical images into 3D physical objects. Among the surgical applications, 3DP technologies has shown promise for uses in education and surgical planning by the fabrication of physical models of complex parts of the human anatomy. The use of 3D printed surgical models has been shown to help shorten operative time, thereby boosting surgical outcomes[10]. Biomodels have been beneficial in various branches of surgery, mainly when the procedures require manoeuvring around delicate neural structures, vessels and organs, and when the appreciation of anatomy can be difficult to attain from 2D radiographic images alone[11]. 3D printed anatomical models were found to improve measurement accuracy significantly in neurosurgery[12-14], cranio-maxillofacial surgery[15, 16], orthopaedics[17, 18], cardio-thoracic and vascular surgery [19-21]. The complex anatomy of the human body and its individual variances make 3D printing ideally suited to allow surgeons to prepare for highly customized procedures by means of custom-designed devices, which can lead to better surgical outcomes, reduction of costs and operative time[22]. Moreover, the combination of reverse engineered data from medical imaging with customized global anatomical shape allows the fabrication of implants with virtually no limits on the complexity of the geometry achievable[23].

In this article, the recent opportunities and advancements of 3D printing technology are explored as it pertains to spinal surgery. We briefly discuss its basic concepts and benefits for the medical setting along with the main areas of application recently achieved in the field of spinal surgery. Figure 1 categorises the four areas in which 3DP has currently found applications: creating models for surgical planning and training; manufacturing custom-tailored drill and screw guide templates; fabricating spinal implants; and developing tissue engineered scaffolds for cartilage repair.

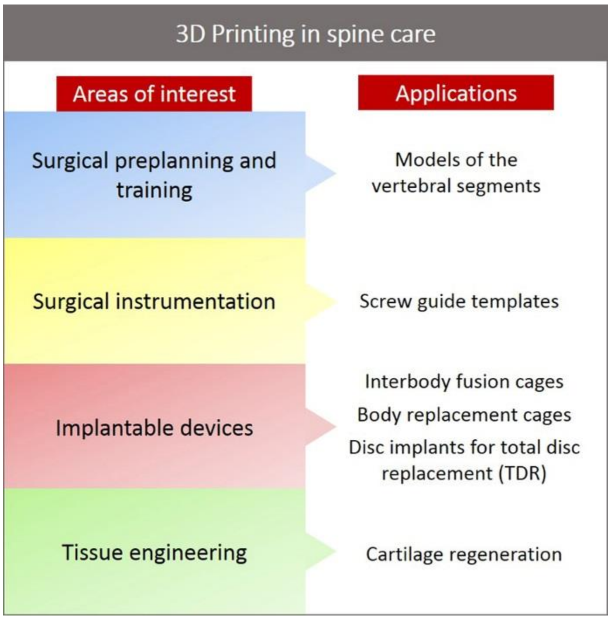

Figure 1 | Diagram of the areas of interest and related applications of 3DP in spine care.

Current challenges and needs for spinal surgery

Current engineered solutions for the surgical treatment of spinal degenerative conditions include implant instrumentation, prosthesis, screws, rods and plates used to facilitate fusion, correct deformities, stabilize, reconstruct or reinforce the spine. Spinal fusion and total disc replacement (TDR) are the two main surgical procedures currently performed when conservative therapies have been unsuccessful.

Intervertebral fusion is performed to stop the motion at a painful vertebral segment. The intervertebral disc is removed and interbody cage implants and bone graft material are inserted to help maintain spine alignment and achieve the fusion between the vertebrae (Figure 2).

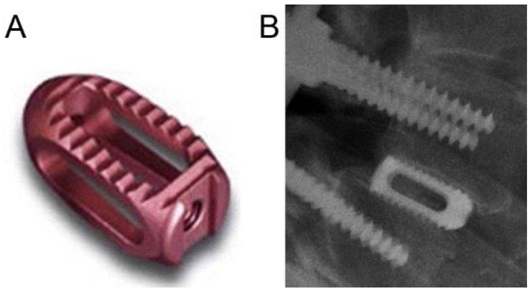

Figure 2 | OIC titanium cage manufactured by Stryker **(A)** and lateral X-ray of a non-migrated OIC cage perfectly fitting the intervertebral disc space **(B)** *Source: reproduced and adapted with permission from Abbushi et al.* [24]**.**

Wide variety of fusion cages are available in the market. They are generally classified into three types: anterior lumbar interbody fusion cages (ALIF); posterior and transforaminal lumbar interbody fusion cages (PLIF/TLIF); direct or extremely lateral interbody fusion cages (DLIF/XLIF). This classification is based on the direction through which the spine is approached for implanting fusion cages. Three materials have primarily been used in the manufacture of cage implants: titanium (Ti), polyetheretherketone (PEEK), and rarely carbon fibre reinforced polymers (CF-P)[25]. Titanium is known as a robust highly biocompatible material; however, because of the material rigidity it may results in stress shielding, which represents one of the main reason for the higher rate of non-union[26, 27]. As an alternative for titanium, PEEK cages have been widely used during the past decade[28-30]. PEEK materials radiolucency and low elastic modulus are attractive attributes that make this material a good candidate for spinal fusion compared with titanium, which may also cause artefacts during medical image acquisition[31]. However, PEEK is known as a bioinert material and further functionalisation with Ti or osteoconductive materials such as hydroxyapatite (HA) may be needed for improving osseointegration[32].

Even though spinal fusion surgery has been widely applied in clinical treatment and the fusion rate has improved remarkably, several postoperative complications, such as adjacent segment degeneration caused by the increasing stress on the facet joints after lumbar fusion with pedicle screw fixation, have to be included in the surgical risks[33]. An alternative to spinal fusion is Total Disc Replacement (TDR) approach, a procedure that aims to treat degenerative disc diseases avoiding adjacent segment degeneration. As oppose to interbody fusion cages, which aim to promote fusion at an early stage, TDR implants are designed to maintain and transmit the axial load to the vertebral endplate throughout the whole patient's life with no bony fusion[34, 35]. The clinical efficacy of disc implants compared to interbody fusion cages has been reported in several recent clinical studies[36, 37]. However, implant subsidence may occur and critical component for success are dependent on patient characteristics, surgeon-related factors and implant sizing[38]. Its clinical efficacy is also questioned, when compared with spinal fusion.

Although spinal fusion cages and disc implants have been widely used for many years, none of the existing clinical devices has shown to be entirely successful and often bone plates and titanium screws are required to enable additional fixation. Standard implants and instrumentations may be unsuitable in some surgical cases, when patient characteristics are crucial to determine the most appropriate solution. Moreover, when spinal reconstruction is required to repair bone defects after tumor resection, fractures or injuries, the artificial body cages should ideally be manufactured at a specific size depending on the defect shape. Expandable cages can be inserted in a compressed form and they do not need to be manufactured at a specific size depending on the patient. However, several studies have shown that they are considerably more expensive to manufacture compared to the older types of vertebral body replacements and that the biomechanical stability of newly developed expandable cages is about equal to that of both non-expandable cages[39, 40]. Therefore, customization is one of the current major priority in orthopaedics and spinal surgery and can be achieved by increasing the number of product sizes or, more accurately, by manufacturing patient-specific implants based on 3D medical images.

Opportunities with 3D printing technology

Generation of 3D objects from medical imaging

The capability to translate data from clinical imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) makes 3D printing technologies particularly useful for many biomedical applications. 3D printing allows an easy conversion of digital models from medical imaging of a patient's anatomy for the fabrication of patient-specific anatomical models and medical implants from various biomaterials, offering a high level of control over the architecture, and guarantees reproducibility. Figure 3 shows the process workflow from image acquisition to the production of 3D printed anatomical models of the patient vertebrae. The image raw data are processed by dedicated 3D modelling software and 3D triangle mesh stereo lithography interface format (STL) and computer-aided-design (CAD) models are generated. The 3D model is further sliced into individual layers by a slicing software, which generate the machine code (e.g. G-Code). Once the 3D model is sliced into the desired number of two-dimensional (2D) sections and translated to the machine proprietary language, the machine reads the data from the CAD drawing and the raw material, in the form of powder, liquid or solid filament, is deposited layer by layer to build up a physical 3D object. The rapid-prototype model is ultimately post-processed.

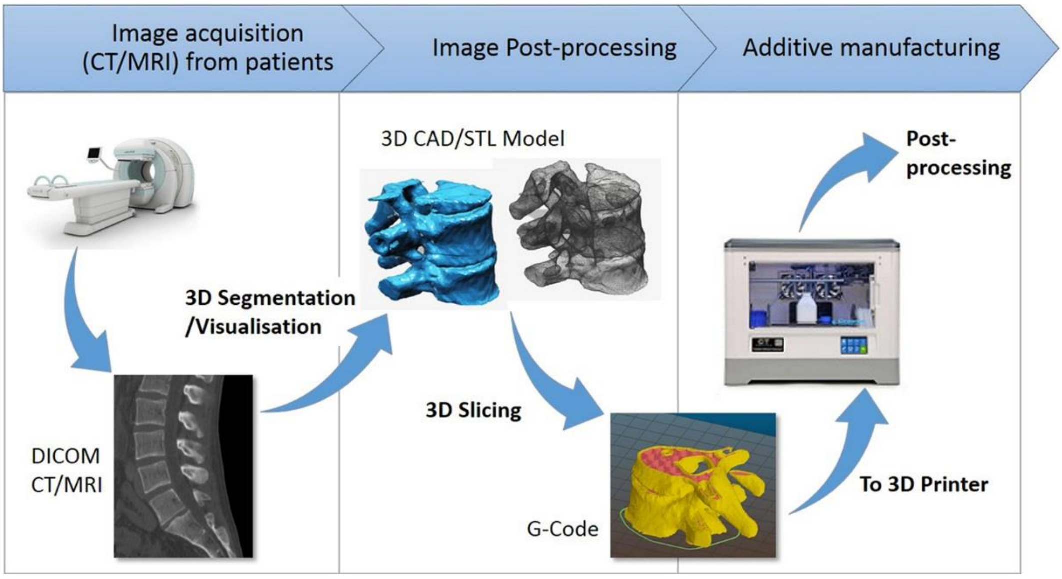

Figure 3 | Process steps involved from image acquisition to the manufacturing of a patient-specific 3D printed model of the spine. DICOM (digital imaging and communications in medicine) images are acquired from patients by computed tomography (CT) or magnetic resonance imaging (MRI). The image raw data are consequently processed by dedicated 3D modelling software. The post-processing involves image segmentation and visualisation and allows the generation of a 3D triangle mesh (STL) and a computer-aided-design (CAD) model of the segmented region of interest. The 3D model is further translated into individual layers by 3D slicing software, which generate the machine code (e.g. G-Code) used for printing. The rapid-prototype model is finally post-processed and the 3D patient-specific model is obtained.

While a range of 3D systems have been developed for industrial use; stereolithography (SLA), multijet modelling (MJM), selective laser sintering (SLS) and fused deposition modelling (FDM) are the main approaches that have been explored for medical applications[41]. Each technique, differ in the manner which layers are built and printing materials used. Every next layer is added to the first layer until the object is fully printed by dispensing the material with an extruder (fused filament), by using a chemical agent (binder) or a laser (sintering/melting), changing the state of the material[42]. Within the resin-based technologies, SLA is widely considered the “gold standard” for medical applications and typically constitutes the more efficient process for larger parts with high levels of build resolution. However, it is significantly more labour intensive and costly in comparison with other 3D printing techniques[43]. Between the powder-based systems, selective laser sintering (SLS) is a laser-based technique that involves a fine powder bed of thermoplastic, metal or ceramic materials. One of its major advantages is the ability to process about any material in a powdered form, including a variety of composite materials such as glass reinforced polymers, metal/polymer composite, metal/metal composites[44]. Other powder-based technologies include direct metal laser Sintering (DMLS) and selective laser melting (SLM), which use concepts comparable to the SLS except that the material is fully melted rather than sintered. Much attention has been paid to extrusion-based systems in recent years since they are mechanically simple and cost-effective processes in comparison to other solid freeform fabrication (SFF) techniques[45]. Fused deposition modelling (FDM) is the most commonly used and affordable extrusion-based technology available currently; however only materials in the form of solid filaments can be processed. Another cluster of 3D printing techniques is constituted by droplet-based systems, such as MultiJet printing (MJM) or PolyJet technology, where the liquid material is deposited in a droplet form. MJM techniques allow high resolution comparable with laser-based systems; however, printing materials used by jetting-based processes are limited and the high price of these printers make this technology more suitable for large- scale production[46].

Customisation of implants and intraoperative instruments

3D printing has been described to provide the possibility to create customized implants for prosthetic operations, rehabilitation, and plastic surgery[47-49]. Numerous medical implants with tailored geometries and physical properties, such as bone fracture fixation devices, parts for artificial hips or knees, nerve guidance channels or prostheses, can be manufactured using 3D printing techniques such as stereolithography[50].

There are many reasons emphasizing the need of customized implants. Firstly, patients outside the standard range of commercially available implants can benefit by means of implant size- or disease-specific special requirements; secondly, surgical outcomes may improve because of individual fitting and adequate match with individual anatomical needs[51]. One of the important features of a spinal implant is that it needs to fit closely to the upper and lower vertebrae endplates to allow the bone to grow into the implant and anchor it in place. Often the standard orthopaedic implants are not sufficient for some patient groups and for the most complex cases, surgeons have limited options and might need to do extra bone graft surgeries[52]. For this reason, most of the manufacturers of spinal implants usually provide for an assortment of cages and disc substitutes in different shapes, sizes and materials. However, very rarely the chosen device fits perfectly into the patient intervertebral space, and several trials with different implant prototypes following x-ray evaluation are needed during the surgery in order to find the best fit. This procedure definitely increases the duration of the surgical intervention with a consequent rise of costs, patient anaesthetic risks and x-ray exposure. In this context, use of 3DP technologies for the fabrication of customized implants provide several opportunities to solve the current interventional issues with direct benefits to the surgical outcomes and patient recovery.

Cost-effectivity and production enhancement

The cost of additive manufacturing technologies has decreased recently because of the advent of low-cost desktop 3D printer and printable multi-materials with flexible characteristics are now commercially available. Another reason lies in the additive manufacturing concept: since the 3D objects are built in a layer-by-layer fashion, no waste of material is required. Additionally, with respect with the clinical field, since custom-designed implants fit patients specifically, they may recover more quickly and are less likely to experience surgical complications and revision surgical procedures, with a significant reduction of time and costs.

The comparatively high speed and low operational cost of the 3D printers means that a large number of models can be produced during the product development phase[53]. As a result, productivity is increasing in terms of the number of cubic centimetres printed per hour, as well as the reliability and repeatability. Traditional manufacturing systems remain less expensive for large-scale production; however, the cost of 3D printing is becoming more competitive for small production runs[54].

Implant designing and optimization

A significant potential of the 3D printing technologies lies within the ability of manufacturing complex geometry implants that are impossible to fabricate with conventional methods. Recent advances in both computational topology optimisation and 3DP have made possible the manufacturing of scaffold constructs with controlled architecture, which may facilitate the process of cell invasion and proliferation, by the designing of hollow geometries and multi-scale porosities. Reproducible irregular internal structures are obtainable with control over pore size, shape and interconnectivity. One way to achieve hierarchical design is to create libraries of unit cells at different physical scales that can be assembled to form scaffold architectures and printed by means of 3DP systems[55]. In this perspective, Finite Element Modelling (FEM) and Analysis (FEA) software allow the simulation of physiological and patient-specific conditions in terms of loads and interactions between the anatomical parts, as well as the possibility to perform topology optimisation for the designing of individually-optimized implants.

3D printing in spinal applications

In spinal surgery, 3D printing can potentially play a significant role in preoperative planning and training; intraoperative guidance with custom-designed drill and screw guide templates; spinal cages for interbody fusion surgery or vertebral body replacement (VBR); disc implants for total disc replacement (TDR); and tissue engineering for cartilage regeneration. We will review each of these applications in following sections.

Models for preoperative planning

Even though the use of 3D printed model for pre-operative planning in spinal surgery is not widely adopted, it has been shown to help shorten operative time, thereby boosting surgical outcomes[10]. Recent work has shown promising results in reducing the operating time and intraoperative blood loss as well as the risk of postoperative complications. Mao et al.[56] recently selected patients with congenital scoliosis, atlas neoplasm, atlantoaxial dislocation, or atlantoaxial fracture-dislocation and used 3D models for observation of the spinal pathoanatomy, surgical planning, and selection of internal-fixation instruments prior to surgical procedures (Figure 4.A). They reported no pedicle penetrations or screw misplacement according to the postoperative planar radiographic images. Ai-Min Wu et al.[57] recently provided a protocol for printing accurate and inexpensive 3D spinal models for surgeons and researchers, by using a FDM apparatus. The resulting 3D printed model is inexpensive and easily obtained for spinal fixation research.

The current 3D-printed models are still not suitable for some surgical procedures where the relationship between anchorage tools and soft tissue is relevant. However, most spinal fixation techniques, including pedicle or lateral screw fixation, which are known to be safe if the screw does not perforate more than 2 mm outside the cortex, could be studied using 3D-printed models. 3D subject-specific prototypes manufactured by stereolitography[58, 59]or selective laser sintering (SLS)[60] have been used to investigate the usefulness of 3D printing in complex spinal surgeries (Figure 4.B). Yang et al.[61] have shown that 3DP technology could reduce the misplacement rate of corrective surgery in the treatment of Lenke 1 adolescent idiopathic scoliosis (AIS). The morphology of complex pathologies can be particularly difficult to assimilate from standard 2D imaging, and 3D printing has shown a potential role in producing accurate models of the spine for assistance in the planning, execution of the surgery and reducing the operating time.

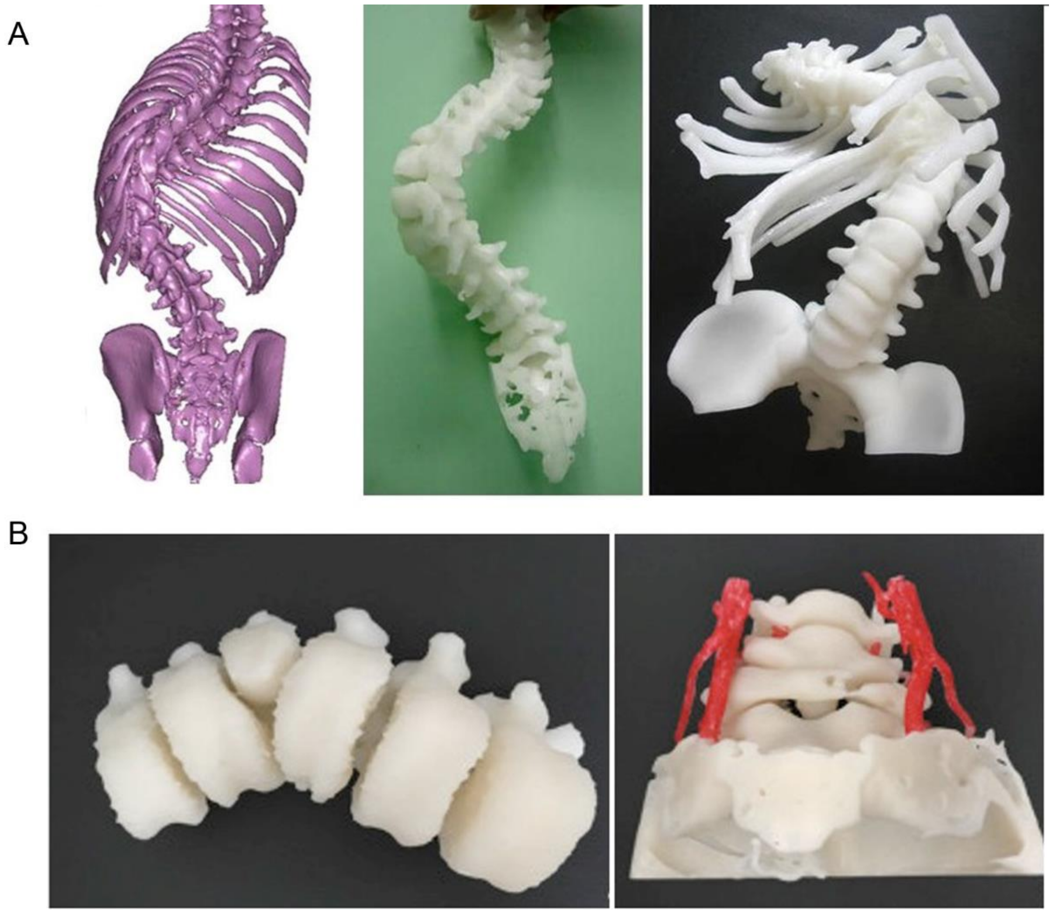

Figure 4 | 3D Printed haptic models of the spine manufactured by different 3DP techniques. Digital spinal 3D reconstruction based on the CT data set and rapid prototyping models of two cases of complex severe spinal deformity made by selective laser sintering (SLS) **(A)**. *Source: reproduced and adapted with permission from Mao et al.*[56] Photosensitive resin 3D models used for observation of the spinal pathoanatomy, surgical planning, and selection of internal-fixation instruments prior to surgical procedures **(B)**. *Source: reproduced and adapted with permission from Wang et al.*[60]

Patient-specific screw guide templates

Use of pedicle screws is the most common and effective procedure used in spinal surgery to stabilise vertebrae. However, placement of screws within pedicle is not always accurate using conventional surgical procedures, which relay mainly on surgeon experience and post-operative evaluation by x-rays. Misplaced screw during surgery carries several risks, which include injuries to the adjacent structures, such as vessels, nerves and viscera.

With the aim of increasing the accuracy of screw placement during spinal surgical procedures, studies have been focus on improving instrumentation by using patient-specific screw guides. Recently, 3D printing of patient-specific guide templates for screw insertion and fixation during spinal surgery procedures have been reported. Several clinical and cadaveric studies have been involved in the evaluation of the placement accuracy of intraoperative screws inserted by means of 3D printed drill guide templates[62-71]. The related instrumentations and outcomes are summarized in

Table 1. Chen et al.[62] have applied 3D printed guide templates manufactured using SLS technique in posterior lumbar pedicle screw fixation. Their results shown that compared with the traditional treatments, the use of intraoperative guidance could shorten the operation time and reduce the amount of haemorrhage. In recent studies[63, 64] three types of templates for precise multistep guidance have been fabricated through a polyjet technology with a patient-specific approach to specifically designed fit and lock templates. The patient-specific guides resulted in increased accuracy and no incidences of perforation, providing a simple and economical method that also allows a reduction of the operating time and radiation exposure of spinal fixation surgery. Accordingly, Merc et al.[66] reported that 3D printed multi-level drill guide templates designed for the dorsal elements significantly lower the incidence of cortex perforation, therefore representing a potential application in clinical practice (Figure 5). Lu et al.[67] have presented a novel computer-assisted 3D printed drill guide template that had to fit into the facet joints on a lock-and-key principle for placement of C2 laminar screws. The reported stereolithographic manufacturing time of the model was about 16 h and the price of each model of the vertebra and navigational template was about $20.

Based on an investigation of the design criteria, material and taking limitation of 3D printing into account, a recent study[72] presented several proposals for improving the spinal drill guides placement accuracy. The design solution proposed consisted in a transparent template, possibly manufactured using stereolithography, which included holes for inserting probes with scales for assessing the correct positioning of the guide on the vertebra. Crawford et al.[73] have patented a 3D printed patient-specific surface-matched template for solving the problem of mis-placement of artificial discs and other surgical implants with minimal effort from the surgeons. Their invention contemplates a computerized tool for planning surgery comprising a haptic interface capable of providing force feedback and provides the surgeon with a custom made 3D printed alignment device created for the particular patient. Their tool can enable correct positioning of artificial discs and other surgical implants and help in pedicle screw trajectory adjustment, anterior plate adjustment, inclusion of adjacent levels within the fusion construct and artificial disc placement.

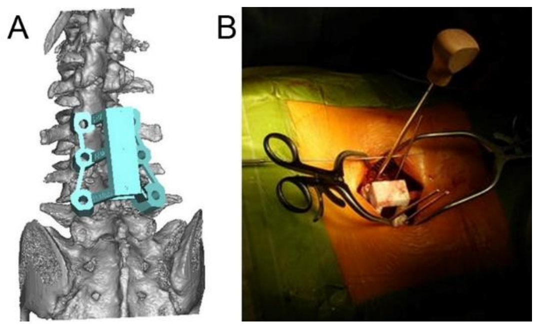

Figure 5 | Designing **(A)** and temporary fixation **(B)** of a multi-level drill guide template that fits onto the dorsal elements of the facet joint. *Source: reproduced and adapted with permission from Merc et al.(2013)[66].*

Table 1 | Clinical and cadaveric studies of 3D printed patient-specific screw guide templates

Year	Authors	Instrument intraoperative application	Material	3D Printing technology	N° of patients - Experimental group	Total N° of screws	Placement accuracy - Experimental group	Placement accuracy – Control group
2015	Chen et al.[62]	Posterior lumbar pedicle screw fixation	Polyamide (PA220)	SLS	20	118	Excellent and good screw placement rate: 100%	Excellent and good screw placement rate: 98.4%
2014	Merc et al.[65]	Pedicle screw placement in lumbar and sacral spine	N/A	SLS	11	72	26% chance of screw misplacement (screw displacement > 3.125 mm or screw tip misplacement > 6.25 mm)	N/A
2014	Kaneyama et al.[63]	Posterior C-2 fixation	Nonsoluble acrylate	POLYJET	23	26	Mean screw deviations: 0.36 mm in the axial plane (range 0.0–3.8 mm) and 0.30 mm in the sagittal plane (range 0.0–0.8 mm)	N/A
2013	Sugawara et al.[64]	Intraoperative screw navigation in the thoracic spine	Nonsoluble acrylate	POLYJET	10	58	Mean screw deviation: 0.87 ± 0.34 mm	N/A
2013	Merc et al.[66]	Lumbar and first sacral pedicle screw placement	Polyamide	SLS	9	10	Displacement sagittal (mm), mean (SD): 0.3 (3.4) Deviation sagittal (°), mean (SD): −1 (5)	Displacement sagittal (mm), mean (SD): 1.5 (3.2) Deviation sagittal (°), mean (SD): −6 (8)
2009	Lu et al.[67]	Placement of C2 laminar screws	Acrylate resin	SLA	9	N/A	No bony breach	N/A
Year	**Authors**	**Instrument intraoperative application**	**Material**	**3D Printing Method**	**N° of cadaveric spines - Experimental group**	**Total N° of screws**	**Placement accuracy - Experimental group**	**Placement accuracy – Control group**
2013	Hu et al.[68]	C2 translaminar screw placement	Acrylate resin	SLA	32	64	Entry point average displacement of the superior and inferior C2TLS in the x, y, z axis was 0.27 ± 0.85, 0.49 ± 1.46, -0.28 ± 0.69, 0.43 ± 0.88, 0.38 ± 1.51, 0.23 ± 0.64 mm	N/A
2012	Ma et al.[69]	Thoracic pedicle screw placement	Acrylate resin	SLA	10	214	Average extent of pedicle violation (x ± s) (mm): 0.95 ± 0.49	Average extent of pedicle violation (x ± s) (mm): 3.29 ± 1.84
2011	Lu et al.[70]	Cervical pedicle screw placement	Acrylate resin	SLA	6	84	82 screws rated as Grade 0 (no deviation), 2 as Grade 1 (deviation of less than 2 mm), and no screws as either Grade 2 or 3 (deviation of more than 2 mm)	N/A
2005	Berry et al.[71]	Cervical, thoracic and lumbar pedicle screw placement	Polyamide	SLS	4	50	Two of the template designs facilitated the placement of 20/20 screws without error	N/A

SLA: Stereolitography; SLS: Selective Laser Sintering.

Spinal implants

3D printing technology is recently emerging as a subject of interest in manufacturing spinal cages for interbody fusion surgery and vertebral body replacement (VBR) as well as disc implants for total disc replacement (TDR).

Within the set of spinal implants, one of the main advantages of additive manufacturing technologies consists of the capacity to fabricate porous geometries, which may derived from structural and topological optimization with the aim of facilitating the process of osseointegration. Moreover, to better match bone stiffness requirements and avoid stress-shielding effects, as well as delivering osteoconductive materials, high porosity is required in case of metallic materials. Hence, with the purpose of reducing stiffness while increasing osteointegration, Lin et al.[74] developed a porous Ti-6Al-4V optimal-structure fusion cage fabricated by SLM process with consistent mechanical properties. The average compressive modulus of the tested caged was 2.97 ± 0.90 GPa, which was comparable with the reported porous tantalum modulus of 3 GPa and therefore provided sufficient compressive strength without excessive stiffness for maintaining spine segmental integrity. Table 2 compares the techniques and the results of recent studies associated with 3D printed interbody fusion cages. 4WEB Medical has recently patented[75] and commercialized innovative 3D printed spine implants that may actively participate in the healing process. The web structure is configured to provide support along at least four planes of the implant to bear against tensile, compressive, and shear forces. The device may provide long-term support of the spine and actively participate in bone growth and healing process through the optimized open architecture, which allows for up to 75% of the implant to be filled with graft material to maximize bone incorporation. Currently, the materials used in the rapid manufacture of commercially available spinal cage implants are titanium and PEEK, typically fabricated by SLS techniques because of the high temperature required for melting the materials. Other solutions for providing appropriate stiffness requirements and osteointegration might be achieved by the use of biomaterials such as polycarbonate (PC). Figueroa et al.[76] have recently presented a new design concept for lumbar spinal surgery implants based on additive manufacturing for the generation of hollow geometries facilitating the process of osseointegration. Their simulation indicates that ABS material is not appropriate for cage implants while PC could provide technical feasibility to lumbar cages that provide the desired requirements in terms of strength and osseointegration.

As an alternative solution to permanent implants, biodegradable cages are receiving increased attention in spinal fusion for reducing revision surgeries by avoiding post-operative complications such as stress-shielding effects and long-term foreign body reaction. In recent studies, optimally designed biodegradable intervertebral fusion cages were fabricated in poly(e-caprolactone) (PCL) mixed with hydroxyapatite (HA) using a selective laser sintering (SLS) solid freeform fabrication machine[77, 78]. Kang et al.[77] developed a multiscale topology optimization technique to balance the complex requirements of load-bearing, stress shielding and interconnected porosity when using biodegradable materials for fusion cages. Figure 6.A shows the topology optimized fusion cage and a 3D printed prototype of the bioresorbable interbody fusion device with integrated multiscale topology optimization. Their PCL intervertebral device demonstrated to achieve the desired stiffness and strength, characteristics needed for better fusion outcomes. The compression tests revealed that the optimal fusion cages could withstand over 3 kN of loads, which is above the physiological level of the human lumbar spine[79, 80]. Based on this work, Knutsen et al.[78] reported the first study focused on the evaluation of the mechanical fatigue properties of bioresorbable PCL cages for cervical spine fusion. They developed two biodegradable cervical cage designs composed of PCL/HA, a porous ring-shaped cage designed based on commercially available cervical fusion cages, and a novel, porous rectangular optimized cage design (Figure 6.B). The optimized design was created using a modular approach, combining a topology optimization approach[81] for the porous regions with image-based design for the cage shape and serrated fixation ridges. Under dynamic testing both designs withstood 5 million (5 M) cycles of compression at 125% of their respective yield forces; however, the measured compressive yield loads fall within the reported physiological ranges. Hence, the tested PCL bioresorbable cages would likely require supplemental fixation. Overall, very few articles have been focus on the application of PCL for fusion cages and more studies need to be done in the context of bioresorbable spinal implants.

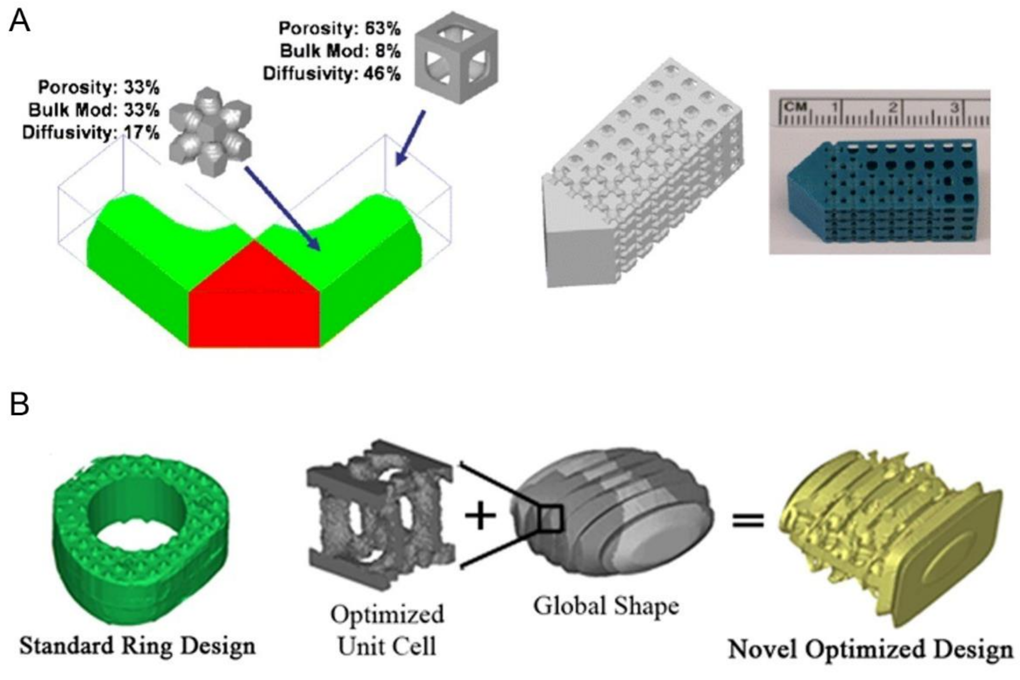

Figure 6 | Porous 3D printed bioresorbable PCL interbody fusion devices with integrated Global-Local Topology Optimization. Design domain and final design of an optimal interbody fusion cage and its fabrication using solid freeform fabrication **(A)**. *Source: adapted from Kang et al. (2010)*[81]. Conventional cylindrical type cervical fusion cage with centre hole for bone graft and topology optimized cervical fusion cage design **(B).** *Source: adapted from Knutsen et al. (2015)*[78].

Most recently 3D printing has been introduced in spinal surgery as a tool for manufacturing individualized fusion implants that replicate the patient-specific topology of the vertebral endplates. Spetzger et al.[82] performed a pilot project of the first implantation with an anterolateral standard approach of a custom-designed cervical titanium cage, made of trabecular titanium and manufactured with direct metal printing (Figure 7). The improved load-bearing surface allowed an accurate fit of the implant and has shown to be promising in decreasing the rate of cage subsidence. However, no mechanical or computational tests are reported for comparison with standard commercially available cervical fusion implants.

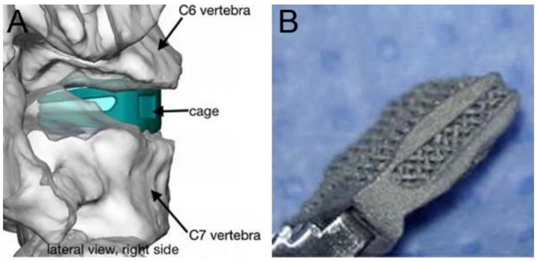

Figure 7 | Virtual **(A)** and actual **(B)** design of a patient-specific titanium fusion cage implant, with a macro- and microcellular trabecular structure for improved osseointegration. *Source: reproduced and adapted with permission from Spetzger et al.(2016)*[82].

In the past 2-3 years, our group has been involved in 3D printing and computational analysis studies of patient-specific spinal implants. A low-cost bioprinting process consisting of a robotic tool enabling a layer-by-layer deposition of polycarbonate (PC) material was used to manufacture a patient-specific cage[83]. Computational models were employed for optimising existing device and design more effective solutions. Figure 8 shows the optimisation of an existing fusion cage by the combination of additive manufacturing and finite element analysis. Different materials such as Ti, PEEK, and PC along with different filling densities were tested. Consistently, stresses increased with reducing material density. Stress peak values were lower than the respective risk of failure in all the simulated cases and the patient-specific design showed lower stress distribution when compared to the conventional cage[84]. Computational analyses along with structural and mechanical testing and biocompatibility studies suggested the feasibility of a lighter, cheaper and patient-specific cage.

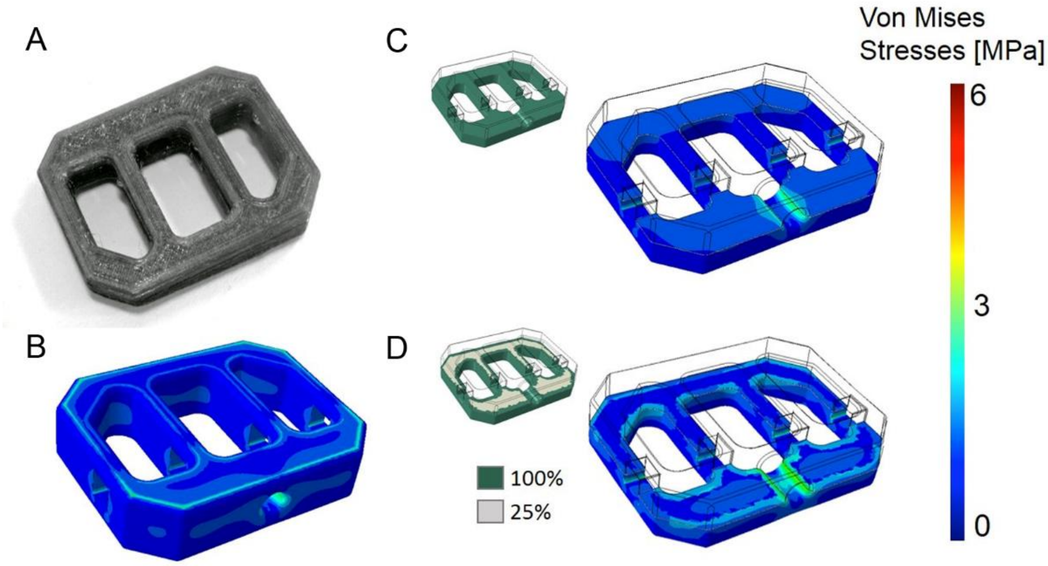

Figure 8 | (A) Photograph of a conventional design 3D printed polycarbonate (PC) fusion cage. **(B-D)** Finite element analysis of the conventional cage under 1 MPa compression: full **(B)** and cut **(C)** view of the distribution of Von Mises stresses for the 100% **(B-C)** and 25% **(D)** filling density design.

Table 2 | Comparison of the results obtained from mechanical and computational testing in studies related to 3D printed interbody fusion cages

Year	Authors	Spinal segment	Cage characteristics	Material	3D Printing technique	Average Compression Young Modulus	Static Compression Standard Loads	Finite element analysis (FEA)	Dynamic Fatigue testing	Conclusions
2015	Knutsen et al. [78]	Cervical	Optimally designed porous biodegradable cage	PCL/4% HA composite	SLS	N/A	•**847 N (Yeld)** •**4000 N** withstood without ultimate failure	N/A	Ultimate Compression Failure Load: **4.5 M cycles (125%)**	Fixation with supplemental devices would likely be required
2013	Kang, et al. [77]	Lumbar	Optimally designed porous biodegradable cage	PCL/4% HA composite	SLS	•Optimized microstructure pore cage: **7548.6 N/mm** •Cylindrical pore cage: **7117.9 N/mm**	•Optimized microstructure pore cage: **2923 N (Yeld)** •Cylindrical pore cage: **3376 N (Yeld)**	•Optimized cage without pore structure, V.Mises max: **8.23 MPa** under 1500 N compression	N/A	Sufficient static mechanical properties to support lumbar interbody loads
2013	Hunt et al.[75]	Lumbar/ Cervical	Web structure including a space truss	Titanium alloy (e.g., γTitanium Aluminide) and other materials contemplated	EBM/SLS /DMLS	N/A	N/A	N/A	N/A	Innovative spine implants with open architecture that allow for up to 75% of the implant to be filled with graft material
2007	Lin et al.[74]	Lumbar	Integrated topology optimization cage design	Ti-Al6-V4	SLM	**2.97 ± 0.90 GPa**	**88.94 ± 1.28 kN (Ultimate)**	N/A	N/A	Comparable stiffness to porous tantalum, providing sufficient compressive strength without excessive stiffness for spine segmental integrity

1 EBM: Electron Beam Melting; DMLS: Direct Metal Laser Sintering; SLA: Stereolitography; SLM: Selective Laser Melting; SLS: Selective Laser Sintering.

Body replacement cages provide a widely accepted alternative to traditional spinal fusion cages for restoring the anterior coloumn height and repairing spinal coloumn defects caused by tumors, fractures and infections[85, 86]. 3D printing technology has been recently explored as a high potetential method to fabricate accurate patient-specific self-stablizing artificial vertebral bodies (SSAVB) for tumor resection and bony reconstruction at the upper cervical spine[87]. The novel customized artificial vertebral body with controlled microstructure has been designed for better biomechanical stability and enhance bone healing and fabricated of porous Ti_6Al_4V using electron beam melting (EBM) technology. The first surgical case of a C2 Ewing sarcoma resection and vertebral body reconstruction (VBR) using the 3D-printed body replacement cage has been recently performed at Peking University Third Hospital's Orthopedics Department[88].

Along with interbody and vertebral body cages, the feasibility of manufacturing disc implants for total disc replacement (TDR) by means of 3DP technologies has been recently studied. Attempts to create a custom-designed conformal intervertebral disc using additive manufacturing technologies were conducted by de Beer et al.[89, 90] Intervertebral disc endplates were successfully designed to overlap the geometry of the vertebra and were manufactured in Ti6Al4V by means of a direct metal laser sintering technology (Figure 9). Domanski et al.[91] have recently conducted a preliminary research of applicability and degree of suitability of 3D printing techniques for the production of intervertebral disc implants. The authors fabricated disc substitute prototypes using different 3DP technologies such as FDM, Inkjet and SLS and patented two new intervertebral disc implants. However, not many attempts have been developed in the computational simulation and design verification of the 3D printed disc implants. Mroz et al.[92] recently developed a new lumbar disc personalized endoprosthesis made of Co28Cr6Mo alloy with the use of selective laser technology. Their results ensured a full reflection of the mechanics and kinematics of the disc and the restoration of a normal height of the intervertebral space and lordotic angle, as well as a full range of mobility of the motion segment in all anatomical planes. Table 3 reports the 3D printing techniques used in recent studies for the fabrication of disc substitutes for total disc replacement (TDR).

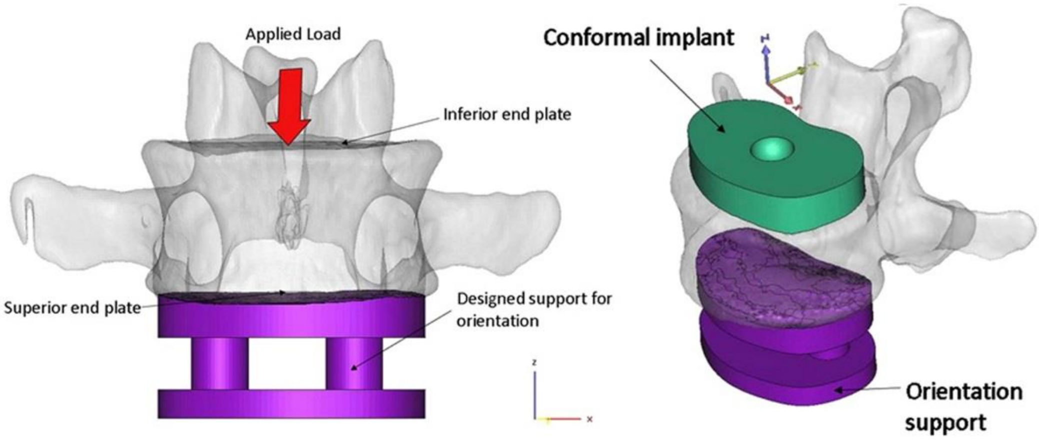

Figure 9 | Custom-made conformal design of a 3D printed Ti spinal implant for total disc replacement (TDR). A support structure was designed to orientate the bone endplate horizontally, perpendicular with respect to the vertically applied pressure. For the designing of the conformal implant a Boolean subtraction operation was performed, followed by an undercut removal function. *Source: reproduced and adapted with permission from de Beer et al (2012).*[89]

Table 3 | Comparison of the rapid prototyping techniques used in different studies for the fabrication of disc substitutes for total disc replacement (TDR)

Year	Authors	Title	Material	3D Printing technique
2015	Mroz et al.[92]	New lumbar disc endoprosthesis applied to the patient's anatomic features	Co28Cr6Mo	SLS
2015	Domanski et al.[91]	Rapid prototyping in the intervertebral implant design process	ABSplus/P430 Thermoplastic	FDM
			N/A	3DP INKJET
			3DP INKJET	SLM
2015	Uden et al.[93]	Custom-tailored tissue engineered polycaprolactone scaffolds for total disc replacement	PCL	FDM
2015	Rosenzweig et al.[94]	3D-Printed ABS and PLA Scaffolds for Cartilage and Nucleus Pulposus Tissue Regeneration	ABS/PLA	FDM
2013	De Beer et al.[90]	Patient-specific intervertebral disc implants using rapid manufacturing technology	Ti6Al4 V	DMLS
2011	Whatley et al.[95]	Fabrication of a biomimetic elastic intervertebral disk scaffold using additive manufacturing	Degradable polyurethane (PU)	Custom-built computed aided 3DP

EBM: Electron Beam Melting; FDM: Fused Deposition Modelling; DMLS: Direct Metal Laser Sintering; SLA: Stereolitography; SLM: Selective Laser Melting; SLS: Selective Laser Sintering.

Tissue engineering for cartilage repair

Cartilage regeneration based on tissue engineered biodegradable scaffolds is another attractive area of interest, which aims to mimic the viscoelastic nature of the native intervertebral disk (IVD) structure. The ideal implanted scaffold should be able to promote cell proliferation and differentiation and to integrate with the native cartilage with the long-term purpose of cartilage repair. Despite several promising studies[96-100], current cartilage tissue engineering strategies are not yet capable of generating new tissue indistinguishable from native cartilage in terms of extracellular matrix composition, structural organization and mechanical properties. Using 3D printing techniques, Bonassar et al.[101] created a tissue-engineered disc construct with cultured ovine nucleus pulposus cells seeded in a central hydrogel with anulus fibrosus cells aligning a collagen matrix circumferentially (Figure 10). With the aim of fabricating elastic scaffolds for intervertebral disc regeneration, Whatley et al.[95] successfully developed a customized 3D printed device made in degradable polyurethane (PU). The technique used consisted in a custom-built computer-aided 3DP technology based on ultra-fine micropipettes that allowed for precise motion and control over the polymer scaffold resolution. Their 3D printed scaffolds exhibited mechanical properties comparable to those of native IVD tissue while mimicking the concentric lamellae morphology of the IVD. Rosenzweig et al.[94] recently proposed the use of inexpensive desktop FDM apparatus for the fabrication of large-pore acrylonitrile butadiene styrene (ABS) and polylactic acid (PLA) scaffolds for nucleus pulposus (NP) tissue regeneration. Mechanical testing showed sustained scaffold stability and preliminary results revealed that the NP cells maintained their individual phenotype over a three-week culture period. FDM technology has also been used by Uden et al.[93] for manufacturing custom-tailored tissue engineered polycaprolactone (PCL) annulus fibrosus scaffolds for total disc replacement. The scaffold constructs were fabricated with nine different submacro- to macro-porosities and the compressive stiffness was higher than that of the human IVD before and after hydration.

Figure 10 | Comparison between a native rat intervertebral disk and a tissue engineered total disk replacement construct. *Source: reproduced with permission from Klein et al. (2014)* [22].

Conclusion

3DP technologies have been an essential tool in spinal research, and have shown promise in clinical applications such as planning, improving accuracies, and providing patient-specific instrumentations. However, there are only few reports related to the applications of personalised 3D printed spinal implants for interbody fusion, vertebral body replacement or total disc replacement. The technology has shown to be feasible for many spinal applications with a significant potential for the development of innovative customized design and surgical procedures. The combination of computational design optimisation with 3D printing technologies allows for the realisation of architecture optimized custom-designed implants and opens the way to promising future surgical solutions. Moreover, the range of printable materials is expanding, and degradability has shown to have several advantages for enhancing bone healing and avoiding stress shielding and long-term foreign body reaction. However, the low mechanical properties of bioresorbable materials may be problematic and future prospective studies are needed for evaluating their continuous reduction in strength under dynamic loading. While 3DP may be cost-efficient, the time needed to produce devices by current 3D technologies still limit its widespread use in hospitals. Therefore, forthcoming studies are needed to investigate the time- and cost-efficacy of this emerging technology for spinal applications. Numerous studies have demonstrated success using tissue engeenering strategies based on the fabrication of 3D printed biodegradable scaffolds and cell-based therapies to treat disc disease and many of these successes are in the early stages of translation into the clinical setting. However, current cartilage tissue engineering strategies are not yet capable of generating new tissue indistinguishable from native IVD. Further invetsitative work is required to replacement nucleus polposus (NP) and annulus fibrosus (AF) tissues for intervertebral disc repair and to enhance cost-effectiveness of medical intervention.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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