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Review

Ceramics in total disc replacements: A scoping review

Lucia Kölle *, Dominika Ignasiak, Stephen J. Ferguson, Benedikt Helgason

Institute for Biomechanics, ETH Zürich, Hönggerbergring 64, 8093 Zürich, Switzerland

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ABSTRACT

Background: Ceramics are used in Total Disc Replacements (1) in articulating surfaces for their wear resistance and biocompatibility and (2) on endplates to promote osseointegration. They furthermore exhibit MRI and CT compatibility. These properties address main challenges associated with non-ceramic Total Disc Replacements *i.e.* wear, migration and postoperative imaging. While brittleness of ceramics caused fear of fracture in the past, improvements of ceramic materials were made and considerable clinical experience with ceramic Total Disc Replacements was gained. This review aims to assess the evidence on the use of ceramics in Total Disc Replacements and compare safety and effectiveness of ceramic Total Disc Replacements to spinal fusion and Total Disc Replacements in general.

Methods: We conducted a scoping review on the use of ceramics in Total Disc Replacements using Scopus, Web of Science and PubMed. The review includes 36 clinical, *ex vivo* and nonhuman *in vivo*, tribological and mechanical studies and case reports.

Findings: Ceramics are used in cervical Total Disc Replacements, with safety and efficacy confirmed in clinical studies, with up to 10 and 3.3 years follow-up, for articulation and osseointegration applications, respectively. Clinical evidence shows that ceramic Total Disc Replacements (alike non-ceramic ones) restore segmental motion and result in non-inferior and possibly superior outcomes to spinal fusion. *In vivo* studies show osseointegration comparable to non-ceramic devices. Tribological studies suggest appropriate wear properties.

Interpretation: We found no indications of systematic problems with the use of ceramics in Total Disc Replacements. Ceramics are suitable materials for Total Disc Replacements.

1. Introduction

Neck and low back pain are the main cause of disability in many countries (Vos et al., 2016). With lifetime prevalences of approximately 40% for low back pain (Manchikanti et al., 2014) and 14–71% for neck pain (Wright et al., 2015), they constitute a serious socioeconomic challenge. A common source of pain is intervertebral disc (IVD) herniation, due to degenerative disc disease (Büttner-Janz et al., 2014) or trauma (Chang et al., 2015). If conservative treatments prove ineffective for 6 months in case of lumbar pain (Büttner-Janz et al., 2014) or 6 weeks in case of cervical pain (Auerbach et al., 2008), invasive treatment is considered.

Two main surgical treatment options are: (1) spinal fusion, in which the vertebrae adjacent to the IVD are permanently connected eliminating motion, and (2) arthroplasty, in which the motion of the spinal segment is preserved through a total disc replacement (TDR). Both treatments are effective, but stricter contraindications make TDRs suitable for fewer patients (43% of cervical (Auerbach et al., 2008) and 5% of lumbar spine surgery patients (Huang et al., 2004)). Although TDRs are related to such challenges as heterotopic ossification and wear debris, they allow faster return to work and less need for postoperative bracing in the cervical spine (Pj and Moatz, 2012) compared to spinal fusion.

Motion preservation by TDR is typically achieved through articulating surfaces, which are prone to wear under repetitive motion and loading. TDRs are particularly attractive for younger patients. However, young patients long remaining lifetime and high physical activity are expected to cause more wear (Pj and Moatz, 2012) which brings high demands on implant materials. Polymeric debris released from metal-on-polymer bearing couples can lead to osteolysis and implant-loosening (Gornet et al., 2017). Metal-on-metal couples have superior wear properties, but elevated metal concentrations and nanodebris can cause local and systemic effects (Gornet et al., 2017). Ceramic-on-ceramic bearing couples produce less wear debris with lower

* Corresponding author.
E-mail address: lucia.koelle@hest.ethz.ch (L. Kölle).

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biological reactivity (Hamadouche and Sedel, 2000). Their high strength, excellent biocompatibility and tribological properties, as well as degradation-resistance, make bioinert ceramics an attractive material for load bearing articulating applications.

Beside wear, implant migration and dislocation are major concerns related to TDRs as this type of complication often requires reoperation (Lou et al., 2018; Ozbek et al., 2017). Achieving primary (initial) and secondary (long-term) stability is of critical importance in preventing such complications. Bioactive ceramics can promote bone ingrowth into TDR endplates and thus secondary stability. For example, osseointegration of silicon nitride is superior to standard biomaterials, such as titanium and PEEK (Webster et al., 2012), as is silicon nitrides biofilm inhibition (Bal et al., 2012; Webster et al., 2012) that might lower the risk of implant-related infections.

Wettability of ceramics makes them an attractive material for articulating surfaces or outer endplates of TDRs, as their self-lubricating properties are expected to reduce adhesive wear (Bierbaum et al., 2002) and wettability enhances osseointegration (Khaskhoussi et al., 2020; Surmeneva et al., 2015; Thian et al., 2010). Furthermore, ceramics are more compatible with MRI and CT imaging than metals, which can cause problematic artifacts or commonly used polymers that are radiolucent.

Despite these promising properties, application of ceramics in TDRs remains limited. One significant concern related to use of ceramics in TDRs is implant fracture due to the brittleness of ceramics. Historically, this concern stems from experience with ceramic hip replacements, which are subject to different loading scenarios than spinal implants, especially in the cervical spine. Furthermore, it has been addressed to some degree by improved manufacturing techniques and improved properties, such as purity, density, grain size and grain distribution (Hamadouche and Sedel, 2000). The current state of knowledge on ceramic TDRs performace and complications remains unclear, as a comprehensive overview of studies performed with ceramic TDRs appears to be missing in the literature.

The main aim of this scoping review is to assess the evidence on the use of ceramics in TDRs. With a scoping review, the scope of a body of literature is accessed. To this end, we compiled clinical, tribological, mechanical, biomechanical and osseointegrative evidence available in scientific literature to compare safety and effectiveness of ceramic TDRs to alternative treatment options, namely spinal fusion and TDRs in general.

2. Methods

The following search string on Scopus (Elsevier) was used to identify literature relevant for the review: *TITLE((replacement* OR nonfusion OR non-fusion OR movement-preserv* OR arthroplasty* OR artificial OR motion-preserv* OR motionpreserv* OR prosthe*) AND (spine OR spinal OR vertebral OR cervical OR lumbar OR intervertebral OR disc OR disk OR IVD)) AND ALL(Ceramic OR Silicon Nitride OR Si3N4 OR silicon-nitride OR Zirconia OR Zirconium dioxide OR zro2 OR calcium phosphate OR bioactive glasses OR Al2O3 OR alumina OR Bioglass OR Hydroxyapatite OR Hydroxylapatite OR aluminumoxide OR Aluminum Oxide OR aluminum-oxide OR aluminiumoxide OR Aluminium Oxide OR aluminium-oxide OR CoC OR ZTA) AND (LIMIT-TO (LANGUAGE, "English"))*.

This resulted in 282 publications (status: September 2021). PubMed and Web of Science were searched with equivalent search strings resulting in additional 38 and 62 publications respectively. All publications were held up against the following exclusion criteria:

- Publications that did not perform a study on ceramic based TDRs intended for humans.
- Study scope and results unrelated to and/or not influenced by ceramics.
- Preliminary results if newer publications of the same study were available.
- Studies that investigated tribology of material pairings without a specific TDR design (such as pin on disc or ball on disc studies).
- Implants that replace not only intervertebral discs, but also vertebrae
- Not peer-reviewed scientific literature

Additional five relevant papers that were not identified by the search strings but were known to the authors, were included. Thus, a total of 36 articles were included in the review. These studies were categorized as clinical (17), *ex vivo* and nonhuman *in vivo* (12), tribological (6) and mechanical (1), see (Fig. 1).

3. Results

The studies included in this scoping review report on 6 TDR devices that use ceramics for articulation and 10 TDRs that use ceramics to promote osseointegration (Table 1). More devices are intended for use in the cervical region (9) than for the lumbar region (7), especially for implants that use ceramics for articulation (4 cervical *vs* 2 lumbar, the latter not reported in clinical studies). In devices with articulating ceramic surfaces, they were made from alumina (3), zirconia (2), silicon-nitride (1), titanium alloy/titanium carbide composite (1) or zirconia toughened alumina (1). These devices were used in the following bearing couples: self-mating ceramics (4), ceramic-on-other-ceramic-material (1), ceramic-on-polymer (1). For osseointegration, devices used TiCaPHA (3) or HA (5) coatings, a coating containing HA or appatite-wollastonite granules (1 TDR in multiple design variations) or HA composite endplates (1) and in some cases, additional HA-composite pins (2).

The 36 articles included in this review report on clinical studies (15) and case reports (2) (Table 2), *in vitro* (2) and *in silico* (4) tribological studies (Table 3), 1 mechanical study (Table 3), and *in vivo* and *ex vivo* nonhuman (8) and human cadaveric studies (4) (Table 4). If controls were used, they were usually fusion (7 clinical and 5 cadveric studies). In five studies another TDR was compared with: 2 nonhuman studies (same coating in different regions or different coatings in same region) and 3 *in silico* tribological studies (same design, different materials).

3.1. Clinical studies

Most clinical studies in this review focused on cervical TDRs with only one case report dedicated to a lumbar device (Table 2). The investigated devices use ceramics for two applications: articulating surfaces and promotion of osseointegration.

3.1.1. Patient outcomes

In the two clinical trials with the longest follow-up time, overall success was found in 74.3% of patients treated at a single level (Gornet et al., 2019a) and 80.4% when treated at two levels (Gornet et al., 2019b) with the same TDR ten years postoperatively (y. p.o.). Here, overall success was defined as improvement of Neck disability index (NDI) $\geq$ 7.5 points, no neurological worsening, no serious adverse events related to implant or implantation (related SAE), no secondary surgery due to treatment failure. With a similar definition, (Guyer et al., 2021) found success in 93% of TDR and 73.6% of fusion patients 2 y. p.o. (NDI improvement value converted to 50 point scale). The percentage of patients who received a ceramic TDR with clinical outcome rated as "excellent" or "good", according to Odom's criteria, ranged from 76% (single level group) (Pimenta et al., 2007) to 100% (Ramadan et al., 2007). Statistically significant superiority of overall success compared to fusion was reported in the few studies that made this comparison (Gornet et al., 2019b; Phillips et al., 2013; Guyer et al., 2021).

Mean reported NDIs range from 6.8 (Guyer et al., 2021) to 14.80 (facet tropism group) (Liu et al., 2021) for TDRs that use ceramics for articulation, and from 5.77 (Shi et al., 2016) to 23.8 (Choi et al., 2012) for TDRs that use ceramics for osseointegration (0–50 scale, converted when reported differently). NDI scores of patients who received TDR

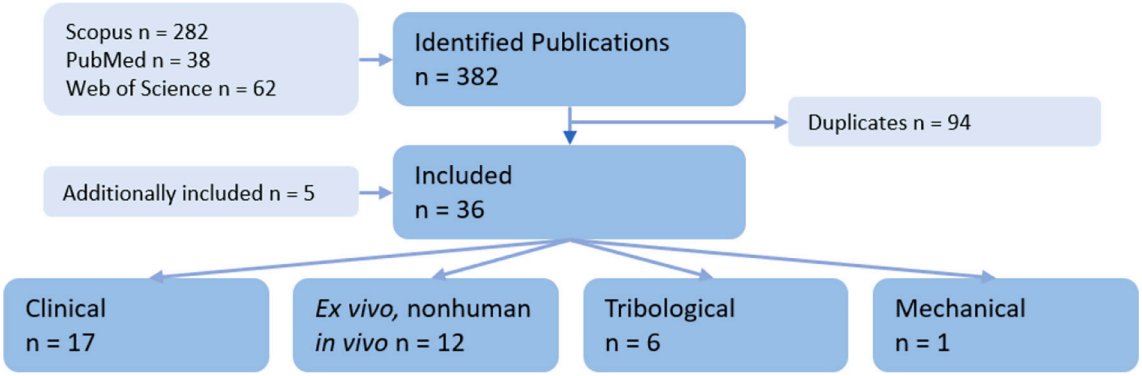

Fig. 1. Publication selection process.

were significantly lower, *i.e.* superior (Geisler et al., 2019; Gornet et al., 2019b; Guyer et al., 2021; Phillips et al., 2013) or not statistically different (Shi et al., 2016), when compared to fusion outcomes.

Mean postoperative neck pain in patients treated with ceramic TDRs, ranged from 13 mm (Ramadan et al., 2007) to 31 mm (Enan et al., 2011) on a 0 mm–100 mm Visual Analog Scale (VAS). Mean reported radicular/arm pain ranged from 5 (Ramadan et al., 2007) to 22 (Enan et al., 2011). Neck pain scores in TDR groups were significantly lower than in patients treated with fusion (Gornet et al., 2019b), however, radicular/arm pain scores were not (Gornet et al., 2019b). There are inter-study methodological variations in the reporting of pain scores: (Enan et al., 2011; Phillips et al., 2013; Ramadan et al., 2007) used a simple VAS scale from 0 mm–100 mm, (Gornet et al., 2019a) used a numeric scale and multiplied duration (0−10) with intensity (0–10) for neck and arm pain, whereas (Gornet et al., 2019b) used numeric ratings based on frequency and intensity. Others did not report arm and neck pain separately but used a single value for both (Choi et al., 2012; Geisler et al., 2019; Guyer et al., 2021) or only improvement (Pimenta et al., 2007).

3.1.2. Complications

The rates of serious adverse events related to implant or implantation (related SAE) reported for ceramic TDRs varied from 0.7% (Guyer et al., 2021) to 7.8% (Gornet et al., 2019a). One study found significantly less related SAE in the ceramic TDR group compared to the fusion group (Gornet et al., 2019b), but another study found no statistical difference (Phillips et al., 2013). Reported rates of secondary surgeries following treatment with ceramic TDR were in the range from <1% (1/148) at 1 y. p.o. (Geisler et al., 2019) to 10.3% at 10 y. p.o. (Gornet et al., 2019a). Compared to patients treated with fusion, patients who received ceramic TDR required significantly fewer secondary surgeries (Gornet et al., 2019b) or there was no statistically significant difference (Phillips et al., 2013).

Case reports present 2 early dislocations of a device using ceramics for osseointegration (Gragnaniello et al., 2013) and one ceramic fracture of a TDR using ceramics for articulation (Nguyen et al., 2011). Implant instability (detectable motion between TDR and bone) was reported in 8% of cases in one study (Skeppholm et al., 2015), anterior migration in 11.7% and migration in 16.7% (Shi et al., 2016) for a TDR using ceramics to encourage osseointegration. They point to (Thaler et al., 2013) that showed that about 60% of this TDRs footprints do not match anatomical size which could lead to migration – explaining this with a design issue, not a material issue. The percentage of patients with grade 3 or 4 heterotopic ossification was reported in a range from 4.4% treated with a TDR using ceramics to enhance osseointegration to 39.0% at either/both of the two levels treated with a TDR using ceramics for articulation (Gornet et al., 2019b). Physiological motion, defined as >5° flexion/extension, was found in only 21% of patients (Choi et al., 2012); ankylosis (no detectable motion) was reported in 5% of cases (Skeppholm et al., 2015) both for TDRs using cermics to improve osseointegration. Incidence of dysphagia was significantly lower in a group treated with a TDR using ceramics to enhance osseointegration than in the fusion control group 2 y. p.o. (McAfee et al., 2010; Phillips et al., 2013) but incidence of dysphonia was similar (McAfee et al., 2010). (Gornet et al., 2017) found titanium concentrations in blood serum to be significantly higher at every time point p.o. than pre.o. in patients treated with a titanium alloy/titanium carbide composite TDR.

3.1.3. Motion

Mean range of motion (RoM) of the operated levels in flexion/extension ranged from 4.9° (3 months p.o.) (Ramadan et al., 2007) to 12.9° (1 and 7 y. p.o.) (Enan et al., 2011; (Swamy et al., 2020), with both values reported for the same TDR device.

3.2. Tribological and mechanical studies (studies without biological specimens)

3.2.1. Tribology

Wear of cervical ceramic TDRs (Table 3) was investigated *in vitro* using spine wear simulators. For a ceramic-on-polymer TDR, idealized, impingement and abrasive wear modes caused mean volumetric wear rates of 0.7 mm^3/MC, 1.5 mm^3/MC, and 2.1 mm^3/MC, respectively with most wear particles originating from PEEK endplates (MC = million cycles) (Siskey et al., 2016). Third body wear of a ceramic coating used in TDRs for osseointegration was investigated and while coated devices produced more wear (1.23 mm^3/MC) than similar devices in which the coating was removed (0.89 mm^3/MC), no third body wear was found in microscopic inspection (Brown and Bao, 2012). The authors speculated that the difference in wear rates could have been due to specimen handling.

Computational tribological studies were performed for lumbar TDRs using ceramics for articulation, in a generic ball-and-socket design, rather than true to detail of a specific product. Wear of lumbar ceramic TDRs was studied *in silico,* using the Finite Element Method assuming linear wear based on Archard's wear theory, volumetric wear calculated from linear wear and geometry adjusted due to linear wear (Shankar and Kesavan, 2015; Shankar and Kesavan, 2016). These studies reported volumetric wear rates ranging from 0.0113 mm^3/MC (Shankar and Kesavan, 2015) to 1.293 mm^3/MC (Shankar and Kesavan, 2016).

In silico tribological studies furthermore investigated factors that influence wear: lubrication regimes (Shaheen and Shepherd, 2007), design optimization for reduced friction (pressure & torque) (Rotaru and Olaru, 2015), effect of radial clearance on wear and contact pressure (Shankar and Kesavan, 2015) and wear in different bearing couples (Shankar and Kesavan, 2016). Low radial clearances (Shankar and Kesavan, 2015), small ball radii (Rotaru and Olaru, 2015) and ceramic-on-ceramic bearing couples (Shaheen and Shepherd, 2007; Rotaru and Olaru, 2015) seem advantageous for lumbar TDRs with low wear.

Table 1
Ceramic TDRs. PEEK = Polyether ether ketone; ZTA = Zirconia Toughened Alumina; HA = Hydroxyapatite; PE = Polyethylene; PET = Polyethylene terephthalate; UHMWPE = Ultra-high-molecular-weight polyethylene; LDPE = Low-density polyethylene; CoCrMo = cobalt-chromium-molybdenum; HA/PLLA = hydroxyapatite/poly-L-lactide composite; TiCaPHA = titanium/calcium phosphate hydroxyapatite coating.

TDR	Materials	Region	Initial Fixation	Secondary Fixation
↓ *Ceramics for articulation* ↓				
Altia TDI™ (Amedica, USA)	silicon-nitride	cervical	keels	
Discocerv® Cervidisc Evolution (Scient'X, France)	alumina, zirconia, titanium	cervical	grooves, teeth	
Prestige LP (Medtronic, USA)	titanium alloy/ titanium carbide composite	cervical	rails	titanium coating
Simplify® Disc (Simplify Medical, Inc., USA)	PEEK, ZTA	cervical	serrated teeth, inline fins	titanium coating
TDR described in (Shaheen and Shepherd, 2007) (Rotaru and Olaru, 2015) (Shankar and Kesavan, 2015) (Shankar and Kesavan, 2016)	alumina; in (Shankar and Kesavan, 2016) also: zirconia	lumbar		
Sofamor Danek (Sofamor Danek, USA)	alumina, titanium	lumbar	grooves	beaded titanium
↓ *Ceramics for osseointegration* ↓				
3DF	UHMWPE coated with LDPE	cervical	pins (HA/PLLA)	unsintered HA coating
Discover (DePuy Spine, USA)	titanium, PE	cervical	spikes	HA coating
NuNec® (Pioneer Surgical, USA)	PEEK, titanium, tantalum markers	cervical	cam blades	HA coating
Porous Coated Motion (PCM) (Cervitech, USA / NuVasive, USA)	titanium alloy, UHMWPE	cervical	teeth	TiCaPHA coating
Pretic-I	titanium alloy, UHMWPE	cervical	serrations	TiCaPHA coating
Charité (DePuy Spine, USA)	CoCrMo, UHMWPE	lumbar	teeth	TiCaPHA coating
fabric TDR described in (Kotani et al., 2006); 3-DF disc (Takiron, Japan)	UHMWPE coated with LDPE	lumbar	pins (HA-PLLA) ((Kotani et al., 2004) (Takahata et al., 2003) without pins)	unsintered HA coating ((Kotani et al., 2004): either sintered HA or apatite-wollastonite)
Maverick (Medtronic Inc., USA)	CoCrMo	lumbar	keels	HA coating
SB Charité (DePuy-Acromed, USA) TDR described in (Gloria et al., 2011)	CoCrMo, UHMWPE; HA-reinforced PE, hydrogel reinforced with PET fibers	lumbar	teeth; pegs	HA coating; HA composite endplates

3.2.2. Mechanical properties

Mechanical testing of a TDR with endplates made of a hydroxyapatite composite with a hydrogel center reinforced with PET fibers lead the authors to conclude that the mechanical behaviour of the device was appropriate (Gloria et al., 2011) (Table 3). Mechanical testing conducted in another study leads the authors of this study to judge the evaluated TDR as appropriate (Shikinami et al., 2010) (Table 4).

3.3. Ex vivo and nonhuman in vivo studies

In vivo and *ex vivo* studies of ceramic TDRs (Table 4) investigated mainly segmental kinematics and/or osseointegration and were based on human cadaveric models with devices implanted postmortem, or nonhuman models (baboon, goats and sheep) with devices implanted *in vivo* and investigated *ex vivo*.

3.3.1. Motion

RoM for flexion/extension in the operated levels ranged from 5.9° (cervical) (Finn et al., 2009) to 8.7° (lumbar) (Kotani et al., 2006) in cadaveric studies using human models. In nonhuman models (sheep, goat, baboon), reported RoM ranged from 3.2° (lumbar) (Kotani et al., 2004) to 7.7° (lumbar) (Cunningham et al., 2003; McAfee et al., 2003). Compared to the intact condition, RoM in flexion/extension was significantly reduced (Hu et al., 2006)), in 2 of 3 investigated groups of (Kotani et al., 2004), significantly increased (Kotani et al., 2005) or not significantly different (Cunningham et al., 2003; McAfee et al., 2003; Shikinami et al., 2010; (Finn et al., 2009; (Kotani et al., 2006).

3.3.2. Osseointegration

Studies defining ingrowth [%] as:"apparent bone contact area/gross total endplate area", reported means in the range from 39% (Cunningham et al., 2009) to 58.65% (Hu et al., 2006). In a study comparing two TDRs with ceramic coating *vs.* sintered titanium beading, mean ingrowth was 47.9% and 54.59%, respectively (Cunningham et al., 2003). The authors of this study judge, that both devices achieved complete osseointegration. Ingrowth over time was also investigated, with reported mean values of 40.51% at 6 m. p.o. and 58.65% 12 m. p.o. (Hu et al., 2006). TDR positioning was reported to affect osseointegration with a reported mean ingrowth values of 44% for optimal *vs* 21% for poor placement, for a cervical device, and 51% for ideal *vs.* 34% for poor placement, in case of a lumbar device, with both TDRs having the same ceramic coating (Cunningham et al., 2009). The tensile failure strength of the implant-bone connection 6 m. p.o. was reported to be significantly lower for the fusion group (0.15 MPa, bioceramic spacer) than for the ceramic-coated TDR group (1.79 MPa) (Takahata et al., 2003).

No device loosening was observed in postmortem implantations in human spines (Kotani et al., 2005; Kotani et al., 2006) or *in vivo* nonhuman studies (Cunningham et al., 2003; Hu et al., 2006; Lou et al., 2017; Takahata et al., 2003). Consequently, no migration (Lou et al., 2017; Cunningham et al., 2003; Kotani et al., 2006; Hu et al., 2006; Kotani et al., 2005) was found. In one study though (Kotani et al., 2004), some implant displacements were reported in the group without additional fixation, however none in the group with temporary fixation.

Table 2
Clinical studies and case reports on ceramic TDRs. p.o. = postoperatively, pre.o. = preoperatively; n = # patients; n_{TDR} = #TDRs; y. = years, m. = months, w. = weeks; Age in years, values are mean, mean (range) or mean ± SD, % of n (if % of n_{TDR} it is indicated) HO = Heterotropic ossification; SAE = Serious adverse events; related SAE = serious adverse events related to implant/implantation; VAS = visual analogue scale (converted to 0-100 mm scale when reported differently);, RoM = range of motion, NDI = Neck disability index (converted to 0–50 scale when reported differently); MMRM = Mixed Model for Repeated Measures.

Reference	Study Type	TDR	Study Description	Follow-up	Region	Patients	Compared with	Results		
								RoM	Clinical Outcome	Related SAE, secondary surgeries, *etc.*
↓ *Ceramics for articulation* ↓										
(Gornet et al., 2019b)	prospective, controlled, randomized, clinical trial	Prestige LP	dual level TDR (adjacent levels)	10 y.	cervical	$n = 209$	dual level fusion, $n = 188$	superior level: 6.6°, inferior level: 5.9°	overall success: 80.4%, fusion: 62.2%; NDI: 7.0, fusion: 11.5; neck pain: 3.8, fusion: 6.5; arm pain: 3.0, fusion: 4.5	related SAE: 3.8%, fusion: 8.1%; secondary surgeries (either operated level): 4.7%, fusion: 17.6%; revision surgeries (either operated level): 0.0%, fusion: 1.4%
(Gornet et al., 2019a)	nonrandomized	Prestige LP	single level TDR	10 y.	cervical	$n = 280$	fusion, $n = 265$ (historical), follow-up: 7 y.	6.85° ± 4.96, fusion: 0.48° ± 0.46	overall success: 74.3%, fusion: 63.2%; NDI: 7.5, fusion: 11.9; neck pain: 11.2, fusion: 19.4; arm pain: 8.5, fusion: 15.0	related SAE: 7.8%, fusion: 5.6%; secondary surgeries (operated level): 10.3%, fusion: 13.6%; revision surgeries (operated level): 0.4%, fusion: 2.1%
(Gornet et al., 2017)	prospective, nonrandomized, study	Prestige LP	single level TDR	7 y.	cervical	$n = 30$				Ti concentrations: significantly higher at every time point p.o. (0.25, 0.5, 1, 2, 3, 5, 7 y. p.o.) than pre.o.
(Liu et al., 2021)	retrospective study	Prestige LP	single level TDR	2 y.	cervical	$n = 90$		facet tropism <7° (symmetry) group: 7.36° ± 3.37 facet tropism >7° (asymmetry) group: 6.39° ± 3.34	Symmetry group: Arm pain (VAS): 18.0 ± 11.2 mm, neck pain (VAS): 23.2 ± 15.4 mm, NDI: 14.20 ± 4.60; asymmetry group: Arm pain (VAS): 17.6 ± 14.8 mm, neck pain (VAS): 21.2 ± 15.1 mm, NDI: 14.80 ± 4.65	effect of facet tropism on RoM
(Enan et al., 2011)	prospective nonrandomized study	Discocerv® Cervidisc Evolution	single or dual level TDR	1.1 y.	cervical	$n = 14$		12.9° ± 2.9	Odom's criteria: excellent or good in 81.6%; NDI: 12.5; neck pain (VAS): 31 mm; radicular pain (VAS): 22 mm	
(Ramadan et al., 2007)	prospective noncomparative study	Discocerv® Cervidisc Evolution	single or dual level TDR	0.4 y.	cervical	$n = 17$		4.9° (0–19)	Odom's criteria: good or excellent in 100% of the cases, NDI: 11 (0–24),	

(*continued on next page*)

Table 2 (*continued*)

Reference	Study Type	TDR	Study Description	Follow-up	Region	Patients	Compared with	Results		
								RoM	Clinical Outcome	Related SAE, secondary surgeries, *etc.*
									neck pain (VAS): 13 mm (0–60), radicular pain (VAS): 5 mm (0−20)	
(Nguyen et al., 2011)	case report	Discocerv® Cervidisc Evolution	dual level TDR, report on ceramic fracture		cervical	n = 1				convex cranial ceramic insert of TDR in inferior level fractured (*ca.* 10 pieces), revision: fusion of both levels, 0.5 y.p.o.: neck and arm pain (VAS): 1/10
(Swamy et al., 2020)	Prospective study	Discocerv	Single and dual level TDR	7 y.	cervical	n_{TDR} = 60; single level: *n* = 44, dual level: n = 8		12.9° ± 2.9	NDI: 10	subsidence (<2 mm): n = 3
(Geisler et al., 2019)	prospective clinical trial	Simplify® Disc	single level TDR	1 y.	cervical	*n* = 148	fusion: *n* = 119 (historical)		NDI (MMRM): 8.25, fusion: 12.55, VAS neck and arm pain (MMRM): 17.5, fusion: 24.8	secondary surgeries: n = 1, fusion: *n* = 1
(Guyer et al., 2021)	prospective, nonrandomized trial	Simplify® Disc	Single level TDR	2 y.	cervical	*n* = 150	fusion: *n* = 117 (historical)	9.6°	NDI: 6.8, fusion: 11.5; neck and arm pain (VAS): 15.6 mm, fusion: 23.3 mm, overall success: 93.0%, fusion: 73.6%	secondary surgery (operated level): 2.7%, fusion: 5.1%; related SAE: 0.7%, fusion: 0.9%
↓ *ceramics for osseointegration* ↓										
(Shi et al., 2016)	retrospective clinical study	Discover	single level TDR	2 y.	cervical	*n* = 60	fusion, *n* = 68	7.91° ± 1.86, fusion: 1.03° ± 0.32	NDI: 5.77 ± 1.24, fusion: 5.66 ± 1.30	
(Skeppholm et al., 2015)	clinical study	Discover	single or dual level TDR	3.33 y.	cervical	n = 28		5.1° (0.2-15.8)	NDI: 2 y. p.o.: 20	ankylosis: 5%; motion between TDR and vertebra: 8%
(Choi et al., 2012)	retrospective review	Porous Coated Motion (PCM)	single or dual level TDR	1.25 y. (median)	cervical	n_{TDR} = 80, *n* = 53		>5°: 21% of n_{TDR}	NDI: 23.8; VAS: 3.1	revision surgery: n = 1
(Pimenta et al., 2007)	prospective nonrandomized study	Porous Coated Motion (PCM)	single and multiple level TDR	2.2 y.	cervical	n_{TDR} = 229, single level: *n* = 71, multiple levels: *n* = 69			Odom's criteria: excellent or good: single level: 76%, multiple levels: 85%; NDI improvement: single level: 37.6%, multiple levels: 52.6%, VAS improvement:	reoperation rates and SAE: single level: n_{TDR} = 3, multiple levels: n_{TDR} = 2

(*continued on next page*)

Table 2 (*continued*)

Reference	Study Type	TDR	Study Description	Follow-up	Region	Patients	Compared with	Results		
								RoM	Clinical Outcome	Related SAE, secondary surgeries, *etc.*
									single level: 58.4%, multiple levels: 65.9%	
(McAfee et al., 2010)	prospective, randomized, clinical trial	Porous Coated Motion (PCM)	single level TDR	2 y.	cervical	$n = 151$	fusion, n = 151			Bazaz Dysphagia Score (none, mild, moderate, severe): 85%, 11.9%, 2.9%, 0, Fusion: 72.4%, 13.8%, 13.8%, 0; incidence of Dysphonia: all visits: 9.03 ±15.4, fusion: 13.1 ± 18.8
(Phillips et al., 2013)	randomized, prospective, controlled, clinical trial	Porous Coated Motion (PCM)	single level TDR	2 y.	cervical	$n = 218$	fusion, $n = 185$	5.7° (0–17.2), fusion: 0.8° (0–6.3)	Odoms criteria: excellent or good: 91.5%, fusion: 86.3%; Overall success: TDR: 75.1%, fusion: 64.9%; NDI 10.9, fusion: 12.75, ≥ 20 mm improvement of VAS: neck pain: 74.3%, fusion: 75.3%; worst arm pain: 79.1%, fusion: 75.3%	related SAE: 5.6%, fusion: 7.4%; Secondary surgeries: 5.2%, fusion: 5.4%
(Gragnaniello et al., 2013)	case report	Maverick	single level TDR: $n = 1$, hybrid: n = 1, report on dislocations		lumbar	n = 2				dislocation 2 w. p.o., TDR removal and fusion, 1 y. p.o.: recovered well

4. Discussion

The aim of this review was to assess the evidence on the use of ceramics in TDRs. To this end, we compiled clinical, tribological, biomechanical, osseointegrative and mechanical evidence reported in 36 scientific publications identified through the systematic literature search. TDRs described in peer-reviewed literature use ceramics for articulation or for osseointegration (a TDR using ceramics to reinforce a polymer can be found in non-peer reviewed literature (Boughton et al., 2001)). Clinical evidence was found to support application of ceramics in TDRs for both articulation and osseointegration, but was limited to largely cervical devices. Tribological and mechanical evidence are promising but sparse. *Ex vivo* and nonhuman *in vivo* studies indicate appropriateness of ceramics for TDRs in the investigated aspects.

4.1. Clinical outcomes

The clinical studies identified and included in this review regard almost exclusively cervical devices; beside a single case report, no clinical studies were found on ceramic TDRs for lumbar spine application. Clinical evidence suggest that ceramic TDRs (alike non-ceramic ones) restore segmental motion and result in non-inferior and possibly superior outcomes to spinal fusion. The use of ceramics does seem to fullfill the basic function of TDRs, to preserve motion of the treated segment. Clinical studies reviewed in this work reported mean RoMs in flexion/extension in a range from 4.9° to 12.9°, which is substantially more than 0.48° to 1.03° reported for fusion controls. Generally, cervical TDRs (ceramic and non-ceramic) provide RoM of 8° on average, which is materially greater than about 1° for RoM after cervical fusion (Findlay et al., 2018).

Reported patient outcomes following treatment with cervical ceramic TDRs were found to be significantly better than after fusion when evaluated as the overall treatment success (Gornet et al., 2019b; Phillips et al., 2013; Guyer et al., 2021), and comparable (Shi et al., 2016) or better (Geisler et al., 2019; Gornet et al., 2019b; Phillips et al., 2013; Guyer et al., 2021) when evaluated using NDI. This is in line with the literature, as significantly more favorable treatment outcomes (Findlay et al., 2018; Hu et al., 2016; Cai et al., 2020) and lower NDI values (Zhang et al., 2015) were reported for cervical TDRs when compared to fusion in previous meta-analyses of randomized controlled trials.

The rates of serious adverse events related to implant or implantation and secondary surgeries were similar (Phillips et al., 2013) or lower (Gornet et al., 2019b) in patients that received ceramic TDRs compared

Table 3
Studies that evaluate the tribology or mechanical properties of TDRs.

Reference	Study Type	TDR	Study Description	Region	Compared with	Results	
						Volumetric Wear	Other results
↓ *tribology: ceramics for articulation* ↓							
(Siskey et al., 2016)	*In vitro*	Simplify® Disc		cervical		idealized: 0.7 ± 0.1, impingement: 1.5 ± 0.4, abrasive: 2.1 ± 0.5	
(Shaheen and Shepherd, 2007)	*In silico*	ball-and-socket; alumina-on-alumina	elastohydrodynamic lubrication theory; ball radii: 14, 21, 28 mm	lumbar	same design made from: Co-Cr-Mo on Co-Cr-Mo, Co-Cr-Mo on UHMWPE		MOM and MOP: boundary lubrication regimes CoC: for ball radius: 14 mm and velocity > 0.9 rad/s: mixed lubrication regime, for 21 mm & 28 mm: potentially fluid-film lubrication
(Rotaru and Olaru, 2015)	*In silico*	ball-and-socket; alumina-on-alumina	ball radii(mm): 8, 10, 12, 14, 16, 18, radial clearance: 0.05 mm	lumbar	same design made from: Co-Cr-Mo on Co-Cr-Mo, Co-Cr-Mo on UHMWPE		increasing ball radius increased frictional torque and decreased maximum pressure; MoM and CoC: higher maximal pressures than MoP MoM: higher frictional torque than MoP and CoC
(Shankar and Kesavan, 2015)	*In silico*	ball-and-socket; alumina-on-alumina	radial clearances: 0.05, 0.1, 0.2 mm	lumbar		radial clearances: 0.05, 0.1, 0.2 mm: 0.01, 0.01, 0.01	increase of radial clearance increases contact pressure; low radial clearance lead to lowest wear
(Shankar and Kesavan, 2016)	*In silico*	ball-and-socket; alumina-on-alumina, zirconia-on-zirconia		lumbar	same design made from: CoCrMo-UHMWPE, 316 SS-UHMWPE, Ti6Al4V-UHMWPE, CoCrMo-CoCrMo, Ti6Al4V-Ti6Al4V	CoCrMo-UHMWPE: 6.34, 316 SS-UHMWPE: 11.18, Ti6Al4V-UHMWPE: 16.72, CoCrMo-CoCrMo: 0.06, Ti6Al4V-Ti6Al4V: 1.98, zirconia-zirconia: 1.29, alumina-alumina: 0.01	
↓ *tribology: ceramics for osseointegration* ↓							
(Brown and Bao, 2012)	*In vitro*	NuNec		cervical	same TDR coating removed	1.23 ± 0.07, control: 0.89 ± 0.08	
↓ *mechanical properties: ceramics for osseointegration* ↓							
(Gloria et al., 2011)	*In vitro*	fiber reinforced hydrogel with HAPEX™ endplates	static and dynamic testing; static: compression, compression-shear, torsion	lumbar	dynamic properties: lumbar porcine IVDs		appropriate mechanical behaviour

All values are mean (range) or mean ± SD, MC = million cycles, MOM = metal-on-Metal, MOP = metal-on-polymer, COC = ceramic-on-ceramic, volumetric wear in mm^3/MC.

to patients treated with fusion. Cervical TDRs in general have been previously reported to be associated with significantly lower rates of related SAE (Hu et al., 2016) and secondary surgeries (Hu et al., 2016; Cai et al., 2020) than fusion. In this context, the results of our review indirectly indicate that complication rates related to ceramic TDRs might be similar or slightly higher than for TDRs in general, even if still comparable or superior to fusion.

In all of the reviewed publications, only one case of ceramic fracture was reported (Nguyen et al., 2011), and may be connected to questionable patient selection (paracentral spur and foraminal stenosis). Although other clinical studies did not explicitly mention ceramic fractures, it is possible that fractures occurred but were counted as adverse events and included in the overall complication rates. However, failures of non-ceramic materials have been reported in articulating and non-articulating TDRs: fractures of polyethylene cores (Kurtz et al., 2007) and rubber tears (Fraser et al., 2004) in lumbar TDRs, cracking of a polyurethane sheath (Fan et al., 2012) tear of a sheath (Clark et al., 2020), disintegration of sheath and artificial annulus (Xia and Winder, 2019) and defect of the artificial annulus-fibers with migration of the artificial core (Brenke et al., 2015) for cervical TDRs.

4.2. Tribological and mechanical studies

The results of this review suggest that wear rates of TDRs with ceramic articulating surfaces are within appropriate range, but evidence in literature is sparse. Mean volumetric wear rates for ceramic-on-ceramic TDRs were reported between 0.0113 mm^3/MC (Shankar and Kesavan, 2015) and 1.293 mm^3/MC (Shankar and Kesavan, 2016) both values reported for lumbar devices investigated with *in silico* models. For a ceramics-on-polymer TDR, up to 2.1 mm^3/MC (Siskey et al., 2016) were reported in the abrasive wear mode *in vitro*. While the range reported for these devices overlaps with the wear rates of TDRs that do not

Table 4
in vivo nonhuman and cadaveric studies investigating biomechanical effects and osseointegration.

Reference	Study Type	Model	TDR	Study description	Region	Subjects	Compared with	Results		
								RoM	Ingrowth	Other results
↓ *Ceramics for articulation* ↓										
(Finn et al., 2009)	*ex vivo*	human	Altia TDI™	single level TDR	cervical	cadaveric specimens: C2/C7; n = 6	intact, fusion	intact: 7.1° ± 2.4, TDR: 5.9° ± 3.1, fusion: 1.5° ± 1.2		
(Dooris et al., 2001)	*ex vivo, in silico*	human	Sofamor Danek	single level TDR; FEM	lumbar	cadaveric specimens: L1/S1; n = 7	intact			load-displacement behaviour of cadaveric specimens and FEM FSU, facet loads of FEM FSU
↓ *Ceramics for osseointegration* ↓										
(Kotani et al., 2005)	*ex vivo*	human	3-DF disc	single level TDR	cervical	cadaveric specimens: Occipital-T2; n = 7	intact, fusion	compared to intact: TDR: 145.2% ± 41.6, autograft: 46.6% ± 32.4, plate: 16.8% ± 10.9		no loosening or dislodgement
(Lou et al., 2017)	*in vivo*	goat	Pretic-I	single level TDR; killing: 6 m. p.o.	cervical	n = 8			42.5% (32.5–54.6)	no subsidence, migration or loosening
(Hu et al., 2006)	*in vivo, ex vivo*	goat	PCM	single level TDR; killing: n = 6: 6 m. p.o., n = 6: 12 m. p.o.	cervical	n = 12	intact	intact: 15.96° ± 0.15, TDR: significantly lower than intact	40.51% ± 24.35 6 m. p.o. and 58.65% ± 28.04 12 m. p.o.	no loosening, no migration, no subsidence, no endplate radiolucencies
(Cunningham et al., 2009)	*in vivo*	PCM: goat, Charite: baboon	Charité; PCM	single level TDR; goats: 6 m. and 12 m. n = 6 killed p.o.; baboons: killed 6 m. p.o.	PCM: cervical, Charité: lumbar	goats: n = 12; baboons: n = 17			cervical: 39% (1–78); lumbar: 46% (2–78); ingrowth depending on TDR placement: cervical: ideal placement: 44% ± 23, suboptimal: 26% ± 33, poor: 21% ± 30; lumbar: ideal: 51% ± 13, suboptimal: 49% ± 19, poor: 34% ± 29	
(Kotani et al., 2006)	*ex vivo*	human	fabric TDR	single level TDR (L4/L5)	lumbar	cadaveric specimens: L1/S1; n = 7	L4/L5: fusion; L2/L3: fabric subtotal disc replacement; L2/L3: fusion	L2/L3: intact: 6.0° ± 1.7; fabric subtotal disc replacement: 8.2° ± 1.4; fusion:1.2° ± 1.0; L4/L5: intact: 7.7° ± 3.2; fabric TDR: 8.7° ± 4.3; cage: 3.4° ± 3.4; cage and pedicle screw instrumentation: 0.7° ± 0.6		no loosening, no dislodgement
(Kotani et al., 2004)	*in vivo, ex vivo*	sheep	fabric TDR	dual level TDR; Group 1: no fixation, Group 2: rod (temporary), Group 3: HA/PLLA rod	lumbar	Group 1: n = 13, Group 2: n = 13, Group 3: n = 10	intact: n = 10	intact: 11.4°, Group 1: 28% of intact; Group 2: 65%; Group 3: 15 and 24 m. p.	trabeculae inserting into fabrics: Group 1:36%, Group 2 (6	Group 1: 6 months p.o.: some displacements without dislodgement;

(*continued on next page*)

Table 4 (*continued*)

Reference	Study Type	Model	TDR	Study description	Region	Subjects	Compared with	Results		
								RoM	Ingrowth	Other results
				(bioresorbable); killing 6, 15, 24 m. p.o.				o.: 49% and 40%	m.p.o.): 63%, Group 3 (24 m.p.o.): 80%	Group 2: 6 m. p.o.: implants in place, Group 3: 6 m. p.o.: all rods broke
(Takahata et al., 2003)	*in vivo*	sheep	3-DF: FABRICUBE	dual level TDR; additonal: rod (Group 1a), 4 and 6 m. p.o.: $n = 4$ killed, HA/PLLA rod (bioresorbable) (Group 1b), 15 and 24 m. p.o.: $n = 4$ killed	lumbar	Group 1a: $n = 8$, Group 1b: $n = 8$	dual level fusion: bioceramic spacers, additonal rod system, n = 4, (Group 2), killing 6 m. p.o.		Group 1a: 4 m. p.o.: 2/4 cases, at 6 m. p.o.: 3/4 cases, Group 1b: all cases, Group 2: 3/4 cases	no loosening
(Shikinami et al., 2010)	*in vivo, ex vivo*	baboons	3-DF disc	single level TDR; killing: 6 m. p.o.	lumbar	n = 8	intact	intact: 6.9° ± 2.9; TDR: 4.9° ± 1.9		
(Cunningham et al., 2003)	*in vivo, ex vivo*	baboons	SB Charité	single level TDR; killing: 6 m. p.o.	lumbar	n = 7	AcroFlex (DePuy-Acromed, USA), n = 10; intact $n = 10$	Intact: 6.93° ± 2.90; SB Charite: 7.71° ± 3.30; AcroFlex: 3.86° ± 1.51	SB Charite: 47.9% ± 8.12, AcroFlex: 54.59% ± 13.24	no loosening, no migration, no lucencies
(McAfee et al., 2003)	*in vivo, ex vivo*	baboons	SB Charité	single level TDR; killing: 6 m. p.o.	lumbar	n = 7	fusion: n = 10 (historical); intact: n = 10	intact: 5.9° ± 2.9; TDR: 7.7° ± 3.3; Fusion: 1.69° ± 1.20	47.9% (35.5–58.8)	no loosening or radiolucency, no migration

Age in years, all values are mean (range) or mean ± SD, n = # subjects; nTDR = #TDRs, y. = years, m. = months, RoM = range of motion, FSU = functional spinal unit.

use ceramics for articulation: 0.26 (Brown and Bao, 2012) - 16.715 mm^3/MC (Shankar and Kesavan, 2016), and ceramic total hip replacements: 0.014–1.015 mm^3/MC (Uddin and Zhang, 2013), the range for non-ceramic TDRs is scattered much wider with wear rates reported as high as 16.715 mm^3/MC (Shankar and Kesavan, 2016) which is about eigth times higher than the highest rate for a ceramic TDR (ceramic-on-polymer, 2.1 mm^3/MC). Even though the reported works addressed all three aspects of tribology: wear, friction and lubrication, the current evidence on tribology of ceramic TDRs is limited by the small number of studies published. Furthermore, only one study evaluated wear of ceramic bearing couples experimentally (Siskey et al., 2016), while other works were performed *in silico*. Computational models of complex multi-factorial phenomena, such as wear, might suffer from assumptions introducing limitations to their predictions. The current evidence indicates that the tribology of ceramic TDRs is suitable, but future work is needed to investigate not only wear rates but also the effects of wear debris from different materials/material pairings.

We judge the level of evidence on ceramic TDRs mechanical properties in scientific literature as very sparse but refer interested readers to "FDA Summary of Safety and Effectiveness Data" documents (FDA Premarket Approval, n.d.) that complement this by offering information on mechanical testing. These documents were not included in this review, as they are not peer-reviewed scientific literature, which is one of the exclusion criteria.

4.3. Ex vivo and non-human in vivo studies

Reported mean RoM in flexion/extension compared to intact showed no clear tendency for hypermobility or loss of mobility of patients receiving ceramic TDRs.

Some TDRs use ceramics to enhance osseointegration. The reviewed *in vivo* nonhuman studies reported mean ingrowth of these devices between 39% (Cunningham et al., 2009) and 58.65% (Hu et al., 2006), whereas for non-ceramic TDRs ingrowth rates were reported between 30.1% (Jensen et al., 2005) and 54.59% (Cunningham et al., 2003). Only one of the reviewed studies compared ingrowth of a ceramic to a non-ceramic TDR, which was in favour of the non-ceramic TDR (54.59% ingrowth *vs.* 47.9%) but the statistical significance of the difference was not reported (Cunningham et al., 2003). Most of the reviewed nonhuman and cadaveric studies reported that no device loosening or dislodgement occurred, except for (Kotani et al., 2004) who reported some implant displacements. These results indicate use of ceramics is rather similar in terms of promoting bone ingrowth, compared to non-ceramic materials used for this purpose. Studies evaluating osseointegration of non-ceramic TDRs appear to be not more abundant than those dedicated to the osseointegration achieved by ceramics.

4.4. Limitations

It is possible that some relevant publications were not identified by our search criteria, *e.g.* if the materials of the investigated TDR were not explicitly reported and thus not found by our search string. While patient selection criteria were stricter in some studies, others included TDRs implanted in complex revision surgeries (Pimenta et al., 2007) or patients that had prior surgeries (McAfee et al., 2010) – no distinction was made between these studies in this review. Generally, varying choice and definitions of outcome measures and greatly varying follow-up time, limits our ability to do a direct inter-study comparison. It was not possible to make distinctions between the single ceramic materials` outcomes as the data was scarce, and only few studies allowed direct comparison between ceramic and non-ceramic TDRs. Studies may have reported on the same cohorts which may create a false impression of greater evidence collected on a certain device where in fact the same samples were analyzed for multiple aspects.

5. Conclusion and future outlook

Ceramics are used for articulation and osseointegration in TDRs for cervical applications, with safety and efficacy confirmed in clinical studies, with up to 10 and 3.3 years follow-up, for articulation and osseointegration applications, respectively.

Tribological and *in vivo* studies suggest promising wear properties

but not advantageous osseointegration properties over non-ceramic designs. Although stronger clinical evidence exists for cervical devices, the number of nonhuman and *in silico* studies on lumbar ceramic TDRs indicates development efforts of TDRs using ceramics also for lumbar applications (that have been generally limited due to past challenges). In conclusion, the current state of knowledge is that the use of ceramics in TDR design does not compromise device properties or performance. Results of pre-clinical studies encourage further research and development of ceramic TDRs for possible improvements in TDR properties and expanding their applications, which would have a great potential in the growing market of motion-preserving spinal treatments. Future studies should focus on addressing the following knowledge gaps: the influence of implant malpositioning on fracture risk (similar to the effect described in ceramic Total Hip Replacements (Goretti et al., 2019)), *in vivo* and *in vitro* characterization of polymer-on-ceramic or different ceramic material pairings, and developing new implant testing methodology, in particular *in vitro* testing capturing adverse scenarios and methods for more accurate assessment of *in vivo* wear.

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Declaration of Competing Interest

Dominika Ignasiak used to be a consultant for NuVasive in the field of computational biomechanics and related clinical studies. The other authors declare no possible conflict of interest.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Stephen Ferguson reports financial support was provided by Horizon 2020. Dominika Ignasiak reports a relationship with NuVasive Inc. that includes: consulting or advisory.

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