ECRI | The Most Trusted Voice in Healthcare

Medical Device Material Performance Study

PEEK Safety Profile

Prepared for
U.S. FDA Center for Devices and Radiological Health

Submitted to

Ed Margerrison, PhD
Director, Office of Science and Engineering Laboratories (OSEL)
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Date of Submission

October 27, 2020

ECRI Corporate Governance:

Michael Argentieri, MS
Vice President, Technology and Safety
margentieri@ecri.org
(610) 316-2766

Karen Schoelles, MD, SM, FACP
Vice President, Clinical Excellence and Safety
kschoelles@ecri.org
(215) 341-3800

Project Manager:

Scott Lucas, PhD, PE
Principal & Director, Accident and Forensic Investigation
slucas@ecri.org
(804) 690-8542

Table of Contents

Table of Tables

Executive Summary

Key Points

1. Searches identified 1,769 citations; 125 articles were selected for inclusion.
2. For local responses to PEEK interbody fusion devices:
    a. Subsidence was the most commonly reported event for cervical and lumbar devices, and it was associated with moderate quality of evidence.
    b. Dysphagia was reported for cervical devices and associated with moderate quality of evidence.
    c. Other local responses for cervical and lumbar fusion devices varied and were associated with low quality of evidence.
3. 80% of the complications reported in ECRI's PSO data were associated with cervical or lumbar fusion devices. 13 of these events resulted in permanent harm, and there were 2 deaths.
4. Evidence gaps:
    a. Systemic response to PEEK devices in included literature. (Note: no animal studies were included in this report, given the volume of human studies of PEEK devices).
    b. Lack of a higher quality of evidence in differentiating risk of PEEK material or general risk of implant procedure for cervical or lumbar fusion devices.
    c. There were no studies on patient and material related factors leading to a host response.
    d. There were only six studies on vertebral body replacement devices and only one study on pedicle fixation devices.
    e. There were no studies evaluating replacement heart valves and mechanical heart valves.

Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review (SR) to identify the current state of knowledge with regard to medical device material biocompatibility. Additionally, data derived from ECRI's patient safety organization (PSO), accident investigations, problem reporting network (PRN), and healthcare technology alerts were analyzed. This report focuses on answering five key questions, provided by FDA and summarized below, regarding a host's local and systemic response to the polymer polyether ether ketone (PEEK). If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

1. What is the typical/expected local host response to PEEK?

Local host responses to PEEK vary depending on the device (interbody fusion cages, cranioplasty plates, other implants) and the target location. ECRI surveillance data revealed infection to be the most common complication. 80% of the complications reported were associated with cervical or lumbar fusion devices. 13 of these events resulted in permanent harm, and there were 2 deaths.

a. *Can responses vary by location or type of tissue the device is implanted in or near*?

i. For PEEK interbody fusion cages, subsidence was the most frequently reported device event in cervical and lumbar locations. Dysphagia was another frequently reported event in the cervical location.
ii. For cranioplasty plates, the event reported in the largest number of studies was exposure, followed by seizures, hematoma, and seroma. Hematoma and seroma may be related to the surgical procedure rather than the PEEK implant.
iii. For other PEEK implants involved in bone fixation, more studies reported hardware malfunctions (including screw loosening, perforation, and malalignment) than any other complications/responses.
iv. For spinal vertebral body replacement, only 2 of 6 studies reported complications (both studies reported subsidence and 1 study reported screw misplacement leading to pain and/or dysphagia).

v. For spinal pedicle fixation, the only available study reported screw loosening and adjacent segment disease that required revision surgery in 25% of patients receiving PEEK rods.
vi. No studies evaluated replacement heart valves and mechanical heart valves.

b. *Over what time course does this local host response appear*?

i. Most dysphagia following cervical interbody fusion was transient and resolved within days or weeks of surgery, but in a few cases may persist up to 24 months.
ii. Subsidence related to spinal implants can occur at any time postsurgery but most cases occurred within the first 12 months.
iii. The timing of other events was unclear in many studies, but clinical assessments were often performed at 6, 12, and 24 months.

2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?

a. What evidence exists to suggest or support this?

No included studies reported systemic manifestations related to PEEK, which suggests that either systemic responses are very rare, or they are not a problem with PEEK devices.

b. What are the likely systemic manifestations?

No studies in the evidence base addressed this question.

c. What is the observed timeline(s) for the systemic manifestations?

No studies in the evidence base addressed this question.

d. Have particular cellular/molecular mechanisms been identified for such manifestations?

No studies in the evidence base addressed this question.

3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

No studies in the evidence base addressed this question.

4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

No studies in the evidence base addressed this question.

5. What critical information gaps exist and what research is needed to better understand this issue?

All gaps listed here could benefit from future research.

i. There were no included studies on systemic response to PEEK devices, suggesting that either systemic responses are very rare, or they are not a problem with these PEEK devices
ii. There was low quality of evidence with regard to local response to cervical or lumbar fusion devices as a function of PEEK or general procedural risk.
iii. There were no included studies on patient and material related factors leading to a host response.
iv. There were only six studies on vertebral body replacement devices and only one study on pedicle fixation devices. There were no studies evaluating replacement heart valves and mechanical heart valves.

Project Overview

FDA engaged ECRI to perform a comprehensive literature search and SR to identify the current state of knowledge with regard to medical device material biocompatibility. Specific materials were selected by FDA based on current priority. For 2020, the following six materials were chosen:

1. Siloxane (Si)
2. Polypropylene (PP)
3. Polyether ether ketone (PEEK)
4. Poly(lactic-co-glycolic acid) (PLGA)
5. Polyurethane (PUR)
6. Polyethylene terephthalate (PET)

The SR was guided by key questions mutually agreed upon by FDA and ECRI. Data were extracted from literature articles and ECRI surveillance databases accordingly.

Key Questions:

1. What is the typical/expected local host response to the material?
    - Over what time course does this local host response appear?
    - Can that response vary by location or type of tissue the device is implanted in or near?
2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?
    - What evidence exists to suggest or support this?
        - In-vivo/clinical studies/reports?
        - Bench or in-vitro studies?
    - What are the likely systemic manifestations?
    - What is the observed timeline(s) for the systemic manifestations?
    - Have particular cellular/molecular mechanisms been identified for such manifestations?
3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
5. What critical information gaps/research are needed to better understand this issue?

If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

Safety Profiles were written for the six materials listed above to include the summary of key findings from the SR and surveillance search and are included in this report.

Literature Search and Systematic Review Framework

The ECRI-Penn Evidence-based Practice Center (EPC) conducts research reviews for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program. ECRI's scientific staff within our Center for Clinical Excellence has authored hundreds of SRs and health technology assessments on 3,500+ technologies/interventions for ECRI's public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and peer-reviewed journals.

For this project, the clinical and engineering literature was searched for evidence related to biocompatibility of each material. Searches of PubMed/Medline and Embase were conducted using the Embase.com platform. Scopus was used initially to search non-clinical literature; however, it was determined that the retrieved citations did not meet inclusion criteria and that database was subsequently dropped from the search protocol. Search limits included publication dates between 2010 and 2020 and English as the publication language. ECRI and FDA agreed on appropriate host and material response search concepts as follows:

- **Material Response**
    - Strength
    - Embrittlement
    - Degradation
    - Migration
    - Delamination
    - Leaching

- **Host Response**
    - Local
        - Inflammation
        - Sensitization
        - Irritation
        - Scarring/fibrosis
            - *Keloid formation*
            - *Contracture*
        - Ingrowth
        - Erosion
    - Systemic
        - Cancer
        - Inflammation
        - Immune Response
        - Fatigue
        - Memory Loss
        - Rash
        - Joint Pain
        - Brain Fog

Search strategies were developed for each concept and combined using Boolean logic. Several search approaches were used for comprehensiveness. Strategies were developed for devices of interest as indicated by the FDA as well as the material-related strategies. Each of these sets were combined with the material and host response strategies. Detailed search strategies and contextual information are presented in Appendix B. Resulting literature was screened by title review, then abstract review, and finally full article review. Data were extracted from the articles meeting our inclusion criteria to address the key questions for each material.

ECRI Surveillance Search Strategy

There are four key ECRI sources for medical device hazards and patient incidents. These databases were searched by key terms and device models. Relevant data were extracted to address the key questions agreed upon by FDA and ECRI. Patient demographics were extracted when available. All data presented were redacted and contain no protected health information (PHI).

ECRI surveillance data comprise ECRI Patient Safety Organization (PSO) event reports, accident investigations, problem reporting network (PRN) reports, and alerts. The PSO, investigations, and PRN reports included in this report include mostly acute patient events. We rarely find chronic conditions or patient follow-up reports, which are more prevalent in the clinical literature. Complications are reported directly by clinical staff, thus reports vary greatly in the level of detail provided.

ECRI PSO

ECRI is designated a Patient Safety Organization by the U.S. Department of Health and Human Services and has collected more than 3.5 million serious patient safety events and near-miss reports from over 1,800 healthcare provider organizations around the country. Approximately 4% of these reports pertain to medical devices. Most of these reports are acute (single event) reports and do not include patient follow-up. These data were filtered by complication, and relevant reports were included in the analysis. "Harm Score" refers to the National Coordinating Council Medication Error Reporting and Prevention (NCC MERP) taxonomy of harm, ranging from A to I with increasing severity (see Figure 1). The entire PSO database was included in the search, with reports ranging from year 2004 through May 2020, unless otherwise noted.

Figure 1. NCC MERP "harm score," which is now regularly used by patient safety organizations.

Category A (No Error)

Circumstances or events that have the capacity to cause error.

Category B (Error, no harm)

An error occurred, but the error did not reach the patient (an "error of omission" does reach the patient).

Category C (Error, no harm)

An error occurred that reached the patient but did not cause patient harm.

Category D (Error, no harm)

An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.

Category E (Error, harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.

Category F (Error, harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.

Category G (Error, harm)

An error occurred that may have contributed to or resulted in permanent patient harm.

Category H (Error, harm)

An error occurred that required intervention necessary to sustain life.

Category I (Error, death)

An error occurred that may have contributed to or resulted in patient death.

Definitions

Harm: Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.

Monitoring: To observe or record relevant physiological or psychological signs.

Intervention: may include change in therapy or active medical/ surgical treatment.

Intervention necessary to sustain life: includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation).

Accident Investigation

ECRI has performed thousands of independent medical-device accident investigations over more than 50 years, including on-site and in-laboratory investigations, technical consultation, device testing and failure analysis, accident simulation, sentinel event and root-cause analyses, policy and procedure development, and expert consultation in the event of litigation. Our investigation files were searched by keywords, and the search was limited to the past 10 years unless we found landmark investigations that are particularly relevant to biocompatibility.

Problem Reporting Network (PRN)

For more than 50 years, ECRI's Problem Reporting Network (PRN) has gathered information on postmarket problems and hazards and has been offered as a free service for the healthcare community to submit reports of medical device problems or concerns. Each investigation includes a search and analysis of the FDA MAUDE database for device-specific reports. Based on our search findings, we may extend our analysis to all devices within that device's FDA-assigned product code. The PRN database was searched by keywords, and the search was limited to the past 10 years.

Healthcare Technology Alerts

We regularly analyze investigation and PRN data to identify trends in use or design problems. When we determine that a device hazard may exist, we inform the manufacturers and encourage them to correct the problem. ECRI publishes the resulting safety information about the problem and our recommendations to remediate the problem in a recall-tracking management service for our members. The Alerts database contains recalls, ECRI exclusive hazard reports, and other safety notices related to Medical Devices, Pharmaceuticals, Blood Products, and Food Products. This database was searched by keywords and specific make and model, and the search was limited to the past 10 years.

Safety Profile - PEEK

Full Name: Polyether ether keytone

CAS Registry Number: 29658-26-2

Search Overview

The SR included clinical and engineering literature on biocompatibility (i.e., host response, material response) of polyether ether ketone (PEEK) used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of PEEK. The devices in Table 1 were recommended by FDA CDRH to guide ECRI in searching this literature and ECRI's surveillance data. In the latter, only those devices listed in Table 1 were included.

Table 1: Medical devices containing PEEK provided by FDA to guide ECRI searches

Regulatory Description	Pro Code	Class
Spinal vertebral body replacement	MQP	II
Intervertebral fusion device with bone graft, lumbar	MAX	II
Intervertebral fusion device with bone graft, cervical	ODP	II
Spinal pedicle fixation	MNI, NKB	II
Plate, fixation, bone	HRS	II
Carnioplasty plate	GWO	II
Replacement heart valve	DYE	III
Mechanical heart valve	LWQ	III

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of PEEK. Inclusion/exclusion criteria and quality of evidence criteria appear in Appendix A in the Appendices document. Due to the number of human studies that addressed the key questions and the relative biocompatibility of PEEK in humans, animal studies were not included in our assessment. Quality of evidence ratings reflected a combination of the quality of comparative data (study designs), quantity of evidence (number of relevant studies), consistency of evidence, magnitude of effect, directness of evidence, and evidence for a dose or time response. The search strategy appears in Appendix B, and a flow diagram documenting inclusion/exclusion of studies appears in Appendix C. Summary evidence tables with individual study data appear in Appendix D, and a reference list of studies cited in the Safety Brief appears in Appendix E.

A summary of our primary findings is shown in Table 2. We then turn to a detailed discussion of research on PEEK as a material as well as research on the various device categories.

Table 2: Summary of primary findings from our systematic review.

Application	**Local host responses or device events**	**Quality of evidence (local responses)**	**Systemic responses**	**Quality of evidence (systemic responses)**
Intervertebral fusion device with bone graft, cervical 52 human studies	Cage subsidence, transient or persistent dysphagia, transient hoarseness, cage migration, nerve root compression, disc herniation, neck pain, wound pain, adjacent disc disease, symptomatic pseudarthrosis, recurrent arm pain, vertebral body collapse, residual stenosis, delayed cervical hematoma, dysphonia,	Moderate for cage subsidence and dysphagia, low for any other responses.	No reported investigation of systemic responses	Very low (no evidence)

Application	Local host responses or device events	Quality of evidence (local responses)	Systemic responses	Quality of evidence (systemic responses)
	C5 palsy, cervical swelling, cerebrospinal fluid leakage, laryngeal nerve palsies, and seroma			
Intervertebral fusion device with bone graft, lumbar 35 human studies	Cage subsidence, cage migration, cage rupture, cage sagging, screw loosening and breakage, adjacent segment degeneration, erectile dysfunction, ileus, retrograde ejaculation, neuroma, seroma, hematoma, paresthesia, motor deficit, lung embolism, hyposensibility, wound disorder, bladder dysfunction, persistent postoperative pain, atelectasis, pleural effusion, aspiration pneumonia, deep vein thrombosis, and vertebral osteolysis	Moderate for cage subsidence, low for other responses	No reported investigation of systemic responses	Very low (no evidence)
Cranioplasty plate 18 human studies	Exposure, hematoma, seizures or new seizures, seroma, subgaleal effusion, cerebrospinal fluid leakage, graft fracture, graft displacement, dehiscence, dural tear, headache, wound problems, necrosis, sinus inflammation, epidural fluid collection, hydrocephalus, and palpable plate	Moderate for exposure and seizures, low for other responses	No reported investigation of systemic responses	Very low (no evidence)
Plate, fixation, bone 13 human studies	Hardware malfunction (screw loosening or perforation, malalignment), extensor tendon irritation, pain, complex regional pain syndrome, stress shielding, poor calcar reduction, tuberosity resorption, avascular necrosis, deep vein thrombosis, and non-union	Moderate for hardware malfunction, low for other responses	No reported investigation of systemic responses	Very low (no evidence)
Spinal vertebral body replacement 6 human studies	Cerebrospinal fluid leakage, screw misplacement (with associated pain and dysphagia), implant subsidence	Low	No reported investigation of systemic responses	Very low (no evidence)
Spinal pedicle fixation 1 human study	Screw loosening and adjacent segment disease requiring revision surgery	Very low	No reported investigation of systemic responses	Very low (no evidence)
Replacement heart valve and mechanical heart valve	No studies identified	Very low (no evidence)	No studies identified	Very low (no evidence)

Intervertebral fusion device with bone graft, cervical: 52 human studies (1 SR,[16] 3 randomized controlled trials [RCTs],[9,10,21] 48 observational studies[1-8,11-15,17-52]). For further information, see Table 1 in Appendix D.

Local host responses or device events: All studies reported on local host reactions potentially related to PEEK cervical fusion devices. Many also reported device events such as cage subsidence or other device malfunctions. The most commonly reported event was cage subsidence (reported for PEEK cages in 18 studies) followed by transient or persistent dysphagia (14 studies). Most dysphagia was transient and resolved within days or weeks of surgery, but in a few cases may persist up to 24 months. Subsidence can occur at any time postsurgery, but most cases occurred within the first 12 months. Other reported local reactions include transient hoarseness, cage migration, nerve root compression, disc herniation, neck pain, wound pain, adjacent disc disease, symptomatic pseudarthrosis, recurrent arm pain, vertebral body collapse, residual stenosis, delayed cervical hematoma, dysphonia, C5 palsy, cervical

swelling, cerebrospinal fluid leakage, laryngeal nerve palsies, and seroma. It is unclear whether some of these outcomes are related to PEEK or the surgical procedure. Pain at donor site occurred only when iliac crest autografts were performed. In general, complication rates were higher for iliac crest autografts compared to PEEK cages. One SR reported a lower rate of subsidence for PEEK cages compared to titanium cages. A retrospective cohort study reported a lower subsidence rate for PEEK cages plus anterior cervical plate compared to PEEK self-locking cages. Another retrospective cohort study reported a lower subsidence rate for the Triad allograft system compared to PEEK cages. One retrospective cohort study reported a higher rate of dysphagia for PEEK cage plus plate (Medtronic) compared to anchored spacer (ROI-C). 13 studies reported no PEEK-related complications; 4 of these studies reported complications related to a comparator device.

Systemic responses: No studies investigated whether there were systemic responses (and by extension no studies reported on factors related to systemic responses).

Overall quality of evidence: Cage subsidence and dysphagia were commonly reported following interbody fusion with PEEK cages; since these were mostly observational studies, the quality of evidence is moderate. The evidence for other local responses or device events is less consistent, so the quality of evidence for these responses is low. No studies reported systemic responses, which suggests that either systemic responses are very rare or they are not a problem with PEEK cages. The quality of evidence for systemic responses is very low.

Intervertebral fusion device with bone graft, lumbar: 35 human studies (4 RCTs,[53,74,79,84] 31 observational studies[54-73,75-78,80-83,85-87]). For further information, see Table 2 in Appendix D.

Local host responses or device events: All studies reported information regarding local host responses. The most common was cage subsidence (18 studies) followed by cage migration (3 studies). Subsidence can occur at any time postsurgery but, as with cervical fusion, most cases occurred within the first 12 months. Other reported local events included cage rupture, cage sagging, screw loosening and breakage, adjacent segment degeneration, erectile dysfunction, ileus, retrograde ejaculation, neuroma, seroma, hematoma, paresthesia, motor deficit, lung embolism, hyposensibility, wound disorder, bladder dysfunction, persistent postoperative pain, atelectasis, pleural effusion, aspiration pneumonia, deep vein thrombosis, and vertebral osteolysis. It is unclear whether some of these events were related to PEEK or the surgical procedure. One RCT reported a lower rate of subsidence for PEEK cages compared to poly (L-lactide-co-D,L-lactide) cages at 12 months post-surgery. One controlled cohort study reported a higher incidence of cage migration with PEEK compared to allograft bone in transforaminal lumbar interbody fusion. Eleven studies did not report any PEEK-related complications or responses.

Systemic responses: No studies investigated whether there were systemic responses (and by extension no studies reported on factors related to systemic responses).

Overall quality of evidence: The evidence for cage subsidence was consistent across several studies, but most studies were observational and the quality of evidence was therefore moderate. For other local symptoms or device events the quality of evidence was low. No studies reported systemic responses, which suggests that either systemic responses are very rare or they are not a problem with PEEK cages. The quality of evidence for systemic responses is very low.

Cranioplasty plate: 18 human studies (5 SRs[88,91,92,94,98] and 13 observational studies[89,90,93,95-97,99-105]). For further information, see Table 3 in Appendix D.

Local host responses or device events: All studies provided information regarding local responses. Those reported in the largest number of studies included exposure (7 studies), hematoma (7 studies), seizures or new seizures (5 studies), and seroma (4 studies). Other reported events included subgaleal effusion, cerebrospinal fluid leakage, graft fracture, graft displacement, dehiscence, dural tear, headache, wound problems, necrosis, sinus inflammation, epidural fluid collection, hydrocephalus, and palpable plate. The timing of complications was not reported in most studies. Complications such as hematoma and seroma may be related to the surgical procedure rather than PEEK plates. One SR compared PEEK to titanium plates and reported significantly lower rates of seizures and subgaleal effusion with PEEK. A cohort study comparing PEEK to titanium plates similarly reported significantly lower rates of new seizures, subgaleal effusion, exposure, and hematoma with PEEK. Another SR found no significant difference in overall complication rates for PEEK vs 3 other types of cranioplasty plates (titanium, hydroxyapatite [HA], and polymethyl methacrylate [PMMA]), but HA and PMMA had higher rates of graft displacement (sometimes requiring

reoperation). A third SR found no difference in complication rates between PEEK, titanium, and autologous bone grafts. In contrast, another SR found higher rates of local complications for PEEK compared to titanium, Norian, and PMMA plates. One cohort study reported lower rates of dural tear for PEEK and titanium compared to PMMA plates. Three studies reported no implant-related complications.

Systemic responses: No studies investigated whether there were systemic responses.

Overall quality of evidence: The evidence supporting exposure or seizures was reported in several studies, and it is plausible that this may be associated with PEEK; however, these events were also reported for other cranioplasty materials and the findings (even from SRs) are from observational studies. Therefore, the quality of evidence for these 2 events is moderate. While hematoma and seroma were reported in several studies, these events are more likely related to the surgical procedure than the cranioplasty material. Other events were reported in fewer studies, so the quality of evidence for other local responses is low. The quality of evidence regarding systemic responses is very low (due to no evidence).

Plate, fixation, bone: 13 human studies[106-118] (all observational designs). For further information, see Table 4 in Appendix D.

Local host responses or device events: All studies reported information related to local events. The most common event was hardware malfunction (screw loosening or perforation, malalignment), reported in 6 studies. Extensor tendon irritation was reported in 2 studies. Other reported events included pain, complex regional pain syndrome, stress shielding, poor calcar reduction, tuberosity resorption, avascular necrosis, deep vein thrombosis, and non-union. These events were rare and reported in only 1 study (but not the same study for all events). The timing of events was unclear in most studies, but clinical assessments were often performed at 6, 12, and 24 months. One study comparing PEEK to titanium found a higher rate of reoperation for screw perforation in the titanium group. Another study reported a higher amount of stress shielding in the PEEK group but a higher rate of tuberosity resorption in the titanium group. Four studies reported no PEEK-related complications.

Systemic responses: No studies investigated whether there were systemic responses.

Overall quality of evidence: The evidence for screw loosening, perforation, and malalignment was reported in several studies, but most studies were observational and the quality of evidence was therefore moderate. For other local symptoms or device events, the quality of evidence was low. The quality of evidence for systemic responses is very low (no evidence).

Spinal vertebral body replacement: 6 studies (1 RCT,[121] 5 observational studies[119,120,122-124]). For further information, see Table 5 in Appendix D.

Local host responses or device events: Two studies reported local events. One study reported one case of cerebrospinal fluid leakage, 3 cases of screw misplacement (leading to pain in 2 cases and dysphagia in 1 case), and implant subsidence (1 case); all events occurred within 3 months postsurgery. The second study reported 1 case of cage subsidence with worsening kyphosis and back pain at 6 months. Four studies reported no PEEK implant-related complications during a mean follow-up ranging from 12 to 28 months.

Systemic responses: No studies investigated whether there were systemic responses.

Overall quality of evidence: Only 2 of 6 studies reported implant-related complications, but this evidence base did not include enough patients to determine the prevalence and variety of different complications. The quality of evidence for local responses or device events was low. For systemic responses, the quality of evidence is very low (none of the studies evaluated potential systemic responses).

Spinal pedicle fixation: 1 retrospective comparative cohort study.[125]

Local host responses or device events: This study reported complications (screw loosening and adjacent segment disease) that required revision surgery in 4 out of 16 patients (25%) receiving dynamic stabilization with PEEK rods. This was a significantly lower rate of revision surgery than that observed for patients receiving rigid stabilization with titanium rods (24/42, 57.1%).

Systemic responses: No studies investigated whether there were systemic responses.

Overall quality of evidence: Based on one small observational study, the quality of evidence for all responses and device events is very low.

Replacement heart valve and mechanical heart valve: Our literature searches did not identify any studies of these devices that met inclusion criteria.

ECRI Surveillance Data

The most common complication reported within surveillance data for PEEK was infection, accounting for approximately 40% of all PSO reports. Additional reported complications are varied and consistent with clinical literature. Most complications that resulted in harm had a harm score of E (27%), requiring temporary intervention, and F (13%), requiring temporary hospitalization. Two deaths associated with fusion devices were reported. All of ECRI alerts were unrelated to host response to PEEK and involved manufacturing, packaging, and device labeling errors.

Patient Safety Organization

Search Results: ECRI PSO identified 1,663 reports of incidents associated with PEEK materials that occurred between 9/2004 and 7/2020. 274 of these involved complications. (see Table 3). 1) Infection - 116 (42.3%), 2) Motor weakness - 24 (8.8%), 3) Hematoma - 23 (8.4%), 4) Clinical Manifestations - 18 (6.6%), and 5) Iatrogenic Injury - 17 (6.2%). The majority of events were associated with harm scores ranging from C through G, with harm to the patient occurring in 46% of the events (Table 4). Harm scores C and D refer to errors that did not cause harm to the patient. E, F, and G resulted in patient harm; incidents with a score of F necessitated initial or prolonged hospitalization and G indicates permanent harm. Complications with vertebral body replacement or fusion devices were most commonly reported.

All individual PSO event reports are redacted and included in Appendix F.

Table 3: Complications in PEEK-related PSO event reports.

Complication	Heart Valve (DYE-LWK)	Plate, Fixation, Bone (HRS-GWO)	Spinal Pedicle Fixation (MNI-NKB)	Vertebral body replacement, fusion device (MQP-MAX-ODP)	Total
Infection		2	6	108	116
Motor weakness			1	23	24
Hematoma	1	2	1	19	23
Clinical manifestations				18	18
Iatrogenic Injury		5	1	11	17
Pain				13	13
Device break/malfunction			6	5	11
Seroma		1	1	9	11
Paralysis			1	9	10
Spinal fluid leak			1	9	10
Hemorrhage	1		1	5	7

Complication	Heart Valve (DYE-LWK)	Plate, Fixation, Bone (HRS-GWO)	Spinal Pedicle Fixation (MNI-NKB)	Vertebral body replacement, fusion device (MQP-MAX-ODP)	Total
Retained foreign body		4	1	1	6
Migration			1	3	4
Paresthesia				2	2
Cord compression				2	2
Total	**2**	**14**	**21**	**232**	**274**

Table 4: Harm score associated with PEEK-related event reports.

Harm Scores (NCC-MERP)		Heart Valve (DYE-LWK)	Plate, Fixation, Bone (HRS-GWO)	Spinal Pedicle Fixation (MNI-NKB)	Vertebral body replacement, fusion device (MPQ-MAX-ODP)	PEEK	Total
A	No Error	--	--	--	33	--	33
B1	Error, No Harm	--	--	--	--	--	--
B2		--	--	--	1	--	1
C		--	1	2	8	1	12
D		1	5	--	20	--	26
E	Error, Harm	1	3	--	69	--	73
F		--	--	--	35	1	36
G		--	1	2	13	--	16
H		--	--	--	--	--	--
I	Error, Death	--	--	--	2	--	2
NULL			4	17	51	3	75
Total		**2**	**14**	**21**	**232**	**5**	**274**

**Harm score was not reported*

Accident Investigations

Search Criteria: Cage, spinal fusion, bone plate, fixation plate, pedicle screw, spinal pedicle fixation, intervertebral fusion device with bone graft (cervical and lumbar), cranioplasty plate, replacement heart valve, and mechanical heart-valve. Investigation files from 2010 were searched to recover cases pertaining to the PP mesh categories provided by FDA.

Search Results: One investigation was recovered as summarized in Table 5. The reported patient incident was likely iatrogenic; however, the investigation was terminated before full inspection of the incident insertor and cage.

This investigation is redacted and included in Appendix F.

Table 5: Accident investigations of patient incidents involving PEEK

Device Type	# Investigations	Reported Problem and Findings (number of investigations)
Spinal Implant (MAX, MQP)	1	Cage "popped off" inserter during implant (1)

ECRI Problem Reports

Search Criteria: PEEK, spinal fusion, cage, plate, screw, cranio, cervical fusion, spacer body, pedicle, and heart valve

Search Results: The search returned 1 report submitted by an ECRI member (Table 6). The report included hardware failure of a spinal pedicle fixation system.

All problems reports are redacted and included in Appendix F.

Table 6: ECRI Problem Report Summary

Device Type	# Problem Reports	Reported Problem (number of problem reports)
Intervertebral fusion device with bone graft, lumbar (MAX)	1	Pain, failed hardware requiring removal

Alerts

Search Criteria: See Appendix F for search terms

Search Results: The search returned 254 manufacturer issued alerts describing problems with labelling, manufacturing, sterility, IFU clarifications, and discontinuation of product, summarized in Table 7.

Table 7: Summary of regulatory and manufacturer alerts

Device Type	# Alerts	Problems
Replacement Heart valve (DYE)	4 All manufacturer-issued	• Packaged with unexpected particulate • IFU error • Discontinuation of product • Manufacturing error

Device Type	# Alerts	Problems
Plate, fixation, bone (HRS)	70 All manufacturer-issued	• Labeling error • Sterility concerns • Manufacturing problem • Packaging error • IFU clarification/update
Cranioplasty plate (GWO)	7 All manufacturer-issued	• Labeling error • Manufacturing problem • Packaging error
Mechanical Heart-valve (LWQ)	3 All manufacturer-issued	• Erroneous distribution of recalled product • Manufacturing problem • IFU clarification
Spinal pedicle fixation (MNI)	10 All manufacturer-issued	• Sterility concern • Manufacturing problems
Spinal pedicle fixation; thoracolumbosacral pedicle screw system (MNI, NKB)	77 All manufacturer-issued	• Manufacturing problems • Labeling error • Sterility concern • IFU clarification
Spinal vertebral body replacement (MQP)	19 All manufacturer-issued	• Manufacturing problems • Labeling error • Sterility concern • IFU clarification • Not 510(k) cleared • Discontinuation of product
Spinal vertebral body replacement; Intervertebral fusion device with bone graft, lumbar (MQP, MAX)	17 All manufacturer-issued	• Manufacturing problems • Labeling error • IFU clarification • Packaged indications of use differ from those approved by Health Canada
Spinal vertebral body replacement; Intervertebral fusion device with bone graft, lumbar Intervertebral fusion device with bone graft, cervical (MQP, MAX, ODP)	6 All manufacturer-issued	• Manufacturing problems • Out of compliance with 510(k) clearance • Labeling error
Spinal vertebral body replacement; Spinal pedicle fixation; thoracolumbosacral	1 Manufacturer-issued	• IFU clarification

Device Type	# Alerts	Problems
pedicle screw system (MQP, MNI, NKB)		
Spinal vertebral body replacement; Intervertebral fusion device with bone graft, cervical (MQP, ODP)	4 All manufacturer-issued	• Manufacturing errors • IFU clarification

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of PEEK. Areas of particular concern involve incidents that result in direct tissue exposure to the material when there is moderate to high-quality evidence of acute or systemic reaction to this exposure, as determined by the SR. Topics with very low or low quality of evidence represent areas of potential gaps in the literature. If the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

No reports meeting inclusion criteria investigated whether there are systemic response to any of the PEEK devices suggested by FDA. This suggests that either systemic responses are very rare, or they are not a problem with these PEEK devices. Below, we discuss additional gaps involving either local responses or device events.

Intervertebral fusion devices with bone graft, cervical and lumbar: While there was evidence of moderate quality for cage subsidence of PEEK intervertebral fusion devices, only one systematic review reported a lower rate of subsidence for PEEK cervical cages compared to titanium cages. Additional research could be indicated to determine whether subsidence is material-related or a result of surgical technique or implant location. There was low quality of evidence for all other reported local host responses or device events, with exception of dysphagia for cervical devices (moderate quality), indicating areas of potential future research. It was unclear from most studies on local response whether the response was related to the material or the procedure.

Cranioplasty plate: Potential complications associated with cranioplasty surgery with PEEK plates are well represented in the literature; however, it is unclear whether the reported local responses (including seizures) are related to PEEK material or the surgery itself. Additional research may be indicated to address this uncertainty.

Plate, fixation, bone: Hardware malfunction was associated with moderate quality of evidence; however, all local host responses and device events were associated with low quality of evidence. These could be areas of potential future research, although the ECRI surveillance data shows little harm associated with these complications. Relative to the spinal PEEK devices, this is less of a concern.

Spinal vertebral body replacement: Only 2 of 6 studies reported implant-related complications, and the associated quality of evidence was low. This is an area where further research is indicated.

Spinal pedicle fixation: There was only 1 human study on pedicle fixation devices, and the associated quality of evidence was low.

Replacement heart valve and mechanical heart valve: There were no studies included on local responses, device events, or systemic responses to heart valves.

Appendix A. Inclusion/Exclusion Criteria and Quality of Evidence Criteria

Inclusion Criteria

1. English language publication
2. Published between January 2010 and August 2020
3. Human studies
4. Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5. Studies that evaluate toxicity/biocompatibility of PEEK or priority devices that include this material

Exclusion Criteria

1. Foreign language publication
2. Published before January 2010
3. Not a study design of interest (e.g., in vitro lab study, case report, narrative review, letter, editorial)
4. Off-topic study
5. On-topic study that does not address a key question
6. No device or material of interest
7. No relevant outcomes (adverse events or biocompatibility not reported)
8. Study is superseded by more recent or more comprehensive systematic review

Quality of Evidence Criteria

1. **Quality of comparison** – is there evidence from systematic reviews including randomized and/or matched study data and/or randomized or matched individual studies?
2. **Quantity of data** – number of systematic reviews and individual studies providing relevant data.
3. **Consistency of data** – are the findings consistent across studies that report relevant data?
4. **Magnitude of effect** – what is the likelihood of adverse effects compared to controls (with no device, lower dosage, shorter exposure time), and possibly number of patients likely to have harms.
5. **Directness of evidence** – do human studies isolate the effect of the device (i.e. can the adverse effects be attributed to the device)?
6. Is there evidence of a **dose response or time response** (e.g. adverse effects increase with longer exposure time)?

Appendix B. Search Summary

Strategies crafted by ECRI's medical librarians combine controlled vocabulary terms and free-text words in conceptual search statements that are joined with Boolean logic (AND, OR, NOT).

Most medical bibliographic databases such as Medline and Embase include detailed controlled vocabularies for medical concepts accessible through an online thesaurus. Controlled vocabularies are a means of categorizing and standardizing information. Many are rich ontologies and greatly facilitate information transmission and retrieval. Frequently seen examples of controlled vocabularies include ICD-10, SNOMED-CT, RxNorm, LOINC, and CPT/HCPCS.

Citations in PubMed are indexed with MeSH terms and those in Embase are indexed with terms from EMTREE. These terms are assigned either by a medical indexer or an automated algorithm. Several terms are selected to represent the major concept of the article – these are called "major" headings. This "major" concept can be included in search strategies to limit search retrieval. The syntax in Embase for this is /mj. We have used this convention in our strategies sparingly since indexing is subjective and we are using a sensitive search approach which errs in the direction of comprehensiveness.

Database providers build functionality into their search engines to maximize the usefulness of indexing. One of the most frequently used shortcuts is term explosion. "Exploding" in the context of hierarchical controlled vocabularies means typing in the broadest (root or parent) term and having all the related more specific terms included in the search strategy with a Boolean OR relationship. We use term explosions whenever feasible for efficiency. Feasibility depends on whether you wish to include all of the related specific terms in your strategy. For example, in one of our approaches we explode the Emtree concept mechanics. This explosion automatically added the all the following terms (n = 174) and their associated entry terms (lexical variants and synonyms) to the strategy using an "OR" without the searcher having to type them in. That's one of the major advantages to searching using controlled vocabularies. We don't rely exclusively on controlled vocabulary terms since there are possible limitations such as inconsistent indexing and the presence of unindexed content. That's why we also include free text words in our strategies.

Set Number	Concept	Search statement
1	**PEEK**	'Polyetheretherketone'/exp
2		'polyetheretherketone' OR 'poly ether ketone' OR 'polyether-ether-ketone'
3		'peek' OR 'peek-It1' OR 'peekIt1' OR 'peek It1' OR 'peek-It2' OR 'peekIt2' OR 'peek It2' OR 'peek-It3' OR 'peekIt3' OR 'peek It3'
4		'polyetheretherketone cage'/de OR 'polyetheretherketone implant'/de
5	**Combine sets**	**#1 OR #2 OR #3 OR #4**
6	Limit by language and publication date	#5 AND [english]/lim AND [2010–2020]/py
7	Limit by publication type	#6 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

Material Response

8		'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'

9		'degradation'/exp OR degradation OR degrad* OR split OR splitting OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR movement OR shift* OR transfer* OR 'delamination'/exp OR delamina* OR leach* OR filtrate OR filter* OR seep*
10		Leachable* OR extractable*
11		(swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat*) NEAR/3 (implant* OR mesh* OR sling* OR tape* OR suture*)
12		'mechanics'/exp [see Emtree explosions section at the end of the strategy]
13		'device material'/exp/mj
14		'Biomedical and dental materials'/exp/mj
15	**Combine sets**	**#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14**

Host Response

16		Host NEAR/2 (reaction* OR response*)
17		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
18		('fibrosis'/exp OR fibrosis OR fibrotic) AND ('postoperative complication'/exp OR implant* OR mesh* OR sling* OR tape*)
19		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj
20		Immun*:ti OR autoimmun*:ti OR hypersens*:ti
21		'inflammation'/exp OR inflamm*:ti
22		'foreign body reaction' OR granuloma*
23		('adhesion'/exp OR 'tissue adhesion'/exp OR 'biomechanics'/exp OR biocompat*)
24		('tissue adhesion'/exp OR adhes*) AND ('postoperative complication'/exp OR implant* OR mesh* OR sling* OR tape*)
25		('erosion'/exp OR 'mesh erosion'/exp OR eros* OR erod*)

26		Expos* AND (implant* OR mesh* OR sling* OR tape* OR suture*)
27		(protrude* OR protrus*) NEAR/3 (implant* OR mesh* OR sling* OR tape* OR suture*)
28		Migrate OR migration
29	**Combine sets**	**#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28**

Alternate Approach

30	By periodical title	(material* OR biomaterial*):jt
31		('physical parameters'/exp/mj OR 'mechanics'/exp/mj) AND ([humans]/lim OR [animals]/lim)
32	**Combine sets**	**#30 AND #31**
33	**PEEK AND Material Response**	**#7 AND #15**
34	**PEEK AND Host Response**	**#7 AND #29**
35	**PEEK AND Alternate Approach**	**#7 AND #32**
36	**Combine all**	**#33 OR #34 OR #35**

Example Embase Explosion

Mechanics/exp

- Biomechanics
- Compliance (physical)
    - Bladder compliance
    - Blood vessel compliance
        - Artery compliance
        - Vein compliance
    - Heart muscle compliance
        - Heart left ventricle compliance
        - Heart ventricle compliance
    - Lung compliance

- Compressive strength
- Dynamics
    - Compression
    - Computational fluid dynamics
    - Decompression
        - Explosive decompression
        - Rapid decompression
        - Slow decompression
    - Gravity
        - Gravitational stress
        - Microgravity
        - Weight
            - Body weight
                - Birth weight
                    - High birth weight
                    - Low birth weight
                        - Small for date infant
                        - Very low birth weight
                            - Extremely low birth weight
            - Body weight change
                - Body weight fluctuation
                - Body weight gain
                    - Gestational weight gain
                - Body weight loss
                    - Emaciation
                - Body weight control
                - Fetus weight
                - Ideal body weight
                - Lean body weight
                - Live weight gain
            - Dry weight
            - Fresh weight
            - Molecular weight
            - Organ weight
                - Brain weight
                - Ear weight
                - Heart weight
                - Liver weight
                - Lung weight
                - Placenta weight
                - Spleen weight
                - Testis weight
                - Thyroid weight
                - Uterus weight
            - Seed weight
            - Tablet weight
            - Thrombus weight
        - Weightlessness
    - Hydrodynamics
        - Hypertonic solution
        - Hypotonic solution
        - Isotonic solution
        - Osmolality
            - Hyperosmolality
            - Hypoosmolality

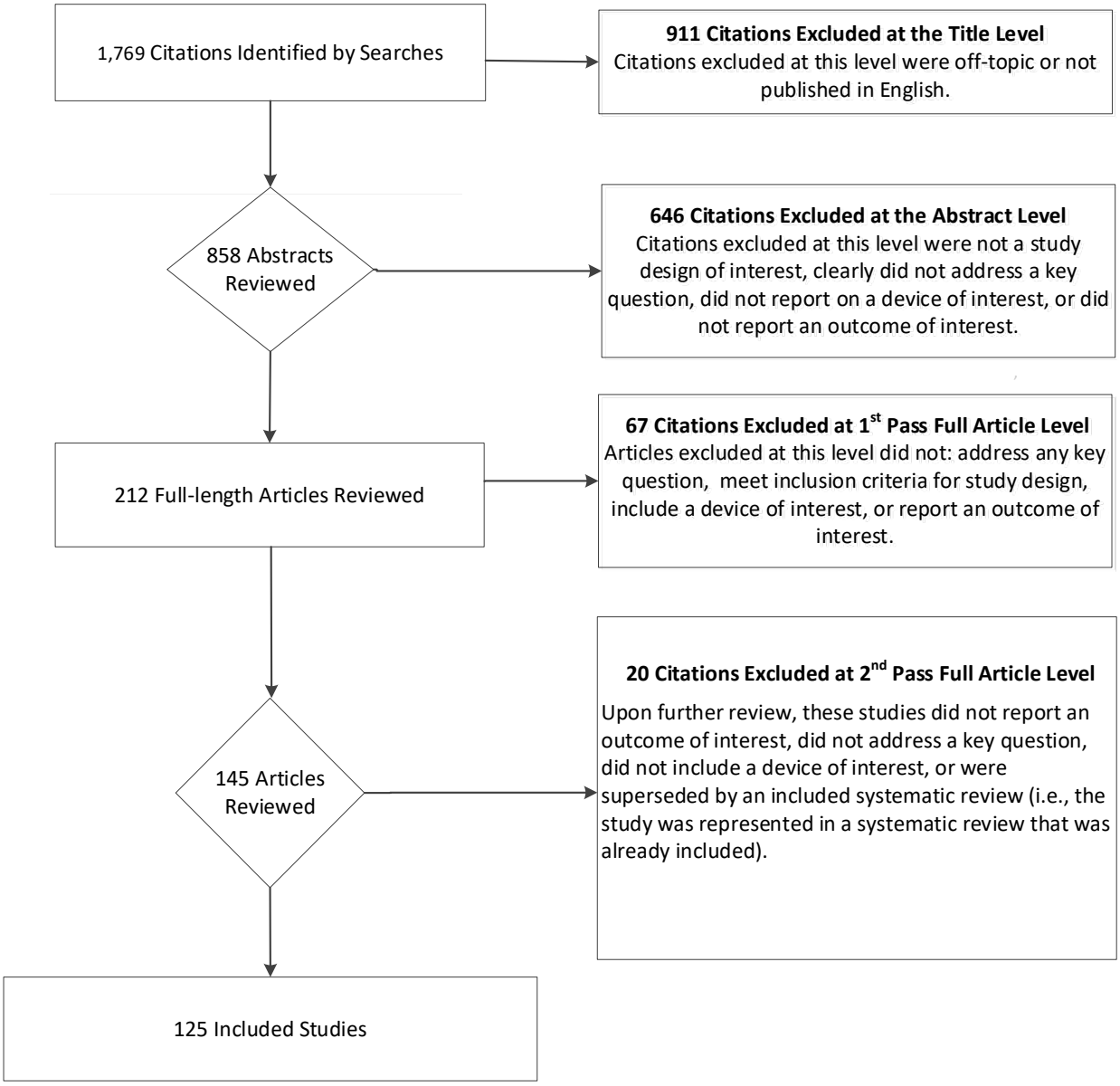
                - Plasma osmolality
                - Serum osmolality
                - Urine osmolality
            - Osmolarity
                - Blood osmolarity
                - Hyperosmolarity
                - Hypoosmolarity
                - Plasma osmolarity
                - Serum osmolarity
                - Tear osmolarity
                - Urine osmolarity
            - Osmosis
                - Electroosmotic
                - Osmotic stress
                    - Hyperosmotic stress
                    - Hypoosmotic stress
        - Photodynamics
            - Photoactivation
                - Photoreactivation
            - Photodegradation
            - Photoreactivity
                - Photocytotoxicity
                - Photosensitivity
                - Photosensitization
                - Phototaxis
                - Phototoxicity
            - Photostimulation
        - Proton motive force
        - Shock wave
            - High-energy shock wave
        - Stress strain relationship
        - Thermodynamics
            - Adiabaticity
            - Enthalpy
            - Entropy
- Elasticity
    - Viscoelasticity
    - Young modulus
- Force
- Friction
    - Orthodontic friction
- Hardness
- Kinetics
    - Adsorption kinetics
    - Flow kinetics
        - Electroosmotic flow
        - Flow rate
        - Gas flow
        - Laminar airflow
        - Laminar flow
        - Powder flow
            - Angle of repose
            - Hausner ration
        - Pulsatile flow
        - Shear flow

        - Thixotropy
        - Tube flow
        - Turbulent flow
        - Vortex motion
        - Water flow
    - Motion
        - Coriolis phenomenon
        - Rotation
        - Vibration
            - Hand arm vibration
            - High frequency oscillation
            - Oscillation
            - Oscillatory potential
            - Whole body vibration
    - Velocity
        - Acceleration
        - Deceleration
        - Processing speed
        - Wind speed
- Mass
    - Biomass
        - Fungal biomass
        - Immobilized biomass
        - Microbial biomass
    - Body mass
    - Bone mass
    - Dry mass
    - Fat free mass
    - Fat mass
    - Heart left ventricle mass
    - Kidney mass
- Materials testing
- Mechanical stress
    - Contact stress
    - Contraction stress
    - Shear stress
    - Surface stress
    - Wall stress
- Mechanical torsion
- Molecular mechanics
- Plasticity
- Pliability
- Quantum mechanics
    - Quantum theory
- Rigidity
- Torque
- Viscosity
    - Blood viscosity
        - Plasma viscosity
    - Gelatinization
    - Shear rate
    - Shear strength
    - Shear mass
    - Sputum viscosity

Viscoelasticity

Appendix C: Study Flow Diagram

I. 1,769 Citations Identified by Searches
    1. **911 Citations Excluded at the Title Level** - Citations excluded at this level were off-topic or not published in English.
    2. 858 Abstracts Reviewed
        a. **646 Citations Excluded at the Abstract Level** - Citations excluded at this level were not a study design of interest, clearly did not address a key question, did not report on a device of interest, or did not report an outcome of interest.
        b. 212 Full-length Articles Reviewed
            i. 67 **Citations Excluded at 1st Pass Full Article Level** - Articles excluded at this level did not: address any key question, meet inclusion criteria for study design, include a device of interest, or report an outcome of interest.
            ii. 145 Articles Reviewed
                1. **20 Citations Excluded at 2nd Pass Full Article Level** - Upon further review, these studies did not report an outcome of interest, did not address a key question, did not include a device of interest, or were superseded by an included systematic review (i.e., the study was represented in a systematic review that was already included).
                2. 125 Included Studies


1,769 Citations Identified by Searches
911 Citations Excluded at the Title Level
Citations excluded at this level were off-topic or not published in English.
858 Abstracts Reviewed
646 Citations Excluded at the Abstract Level
Citations excluded at this level were not a study design of interest, clearly did not address a key question, did not report on a device of interest, or did not report an outcome of interest.
212 Full-length Articles Reviewed
67 Citations Excluded at 1st Pass Full Article Level
Articles excluded at this level did not: address any key question, meet inclusion criteria for study design, include a device of interest, or report an outcome of interest.
145 Articles Reviewed
20 Citations Excluded at 2nd Pass Full Article Level
Upon further review, these studies did not report an outcome of interest, did not address a key question, did not include a device of interest, or were superseded by an included systematic review (i.e., the study was represented in a systematic review that was already included).
125 Included Studies

Appendix D. Evidence Tables

Table 8: . Intervertebral Fusion Device with Bone Graft, Cervical – Health Effect (In Vivo)

Human Studies

Local Response/Toxicity

Source Citation: Ahmed and Galal 2020[1]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cage vs dynamic cervical implant (DCI, titanium)

Contact Duration: 12 months

Dose: Single level

Frequency/Duration: Single administration

Response: No PEEK-related complications (only complications in DCI group)

Patient characteristics (gender, mean age): 67% male, 47 years

Number per group: 15 PEEK, 15 DCI

Observations on adverse effects: No PEEK-related complications (only complications in this group were related to surgery); 3 patients in DCI group had implant migration that caused severe dysphagia and recurrent neck pain. Subsidence was greater in the DCI group

Timing of adverse effects: Implant migration at 4-6 weeks, subsidence at 3 and 12 months

Factors that predict response: NR

Source Citation: Ashour et al. 2020[2]

Study Design: Retrospective cohort study

Device or Material: PEEK cage

Contact Duration: 24 months

Dose: 4 levels

Frequency/Duration: Single administration

Response: Cage migration, Cage subsidence

Patient characteristics (gender, mean age): 53% male, 48 years

Number per group: 66

Observations on adverse effects: No complications, but 3 cases of asymptomatic cage migration and 3 cases of asymptomatic subsidence occurred

Timing of adverse effects: During 24 month follow-up

Factors that predict response: NR

Source Citation: Khattab and Kotb 2020[3]

Study Design: Prospective controlled cohort study

Device or Material: Stand-alone PEEK cage (Tryptik CA) vs PEEK PREVAIL anchored cage

Contact Duration: 24 months

Dose: Single level

Frequency/Duration: Single administration

Response: Postoperative dysphagia

Patient characteristics (gender, mean age): 62% female, range 44-60 years

Number per group: 21 stand-alone PEEK, 29 PEEK PREVAIL

Observations on adverse effects: There were no adjacent level pathology, pseudarthrosis, or implant-related; however, postoperative dysphagia occurred in 2 patients (6.8%) in group 1 (stand-alone PEEK) and three patients (10.3%) in group 2 (PEEK PREVAIL), all of whom improved spantaneously with follow-up

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Moo et al. 2020[4]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cages (Cornerstone, Cervios, Solis) vs Triad allograft system

Contact Duration: 24 months

Dose: Double level

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 52.3%, male, 54 years

Number per group: 35 PEEK, 53 allograft

Observations on adverse effects: No complications were reported in either group. However, the subsidence rates were 30% (21/70) and 11% (12/104) in the PEEK and allograft groups, respectively ($p < 0.05$)

Timing of adverse effects: NR

Factors that predict response: PEEK associated with higher subsidence rate

Source Citation: Yang et al. 2019[5]

Study Design: Prospective controlled cohort study

Device or Material: PEEK cage vs allograft interbody cage (BioCage)

Contact Duration: Mean: 29.68 months (range 12-40 months)

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Minor dysphagia

Patient characteristics (gender, mean age): 55% male, 50.4 years

Number per group: 49 PEEK, 58 BioCage

Observations on adverse effects: 2 and 4 patients (3.45% BioCage, 8.16% PEEK) complained of minor dysphagia with a duration of 5 to 7 days respectively, but all cases were resolved at 12 months

Timing of adverse effects: early postoperative period

Factors that predict response: NR

Source Citation: Godlewski et al. 2018[6]

Study Design: Cohort study

Device or Material: PEEK cage (Aesculap CeSpace)

Contact Duration: 12 months

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): NR

Number per group: 100

Observations on adverse effects: Cage subsidence observed in 18/176 (10.23%) operated disc spaces, but subsidence was not correlated with clinical outcomes

Timing of adverse effects: within 12 months

Factors that predict response: Most subsidence occurred at C6/C7 level (9/18) or C5/C6 level (7/18).

Source Citation: Hu et al. 2018[7]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cage vs nano-hydroxyapatite/ polyamide66 (nHA/PA66) cage

Contact Duration: 7 years

Dose: Single level

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 54% male, 51.9 years

Number per group: 51 PEEK, 47 nHA/PA66

Observations on adverse effects: Cage subsidence rates were 9.8% (PEEK) and 10.6% (nHA/PA66)

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Junaid et al. 2018[8]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cage vs titanium cage

Contact Duration: 12 months

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Pain at donor site

Patient characteristics (gender, mean age): 65.8% male, 36 years years (PEEL), 45.9 years (titanium)

Number per group: 65 PEEK, 84 titanium

Observations on adverse effects: 4 (2.6%) patients in PEEK cage group and 2 (1.3%) in titanium cage group complained of pain at the donor site (iliac crest).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Arts et al. 2017[9]

Study Design: RCT

Device or Material: PEEK cage vs porous silicon nitride spacers

Contact Duration: 24 months

Dose: Single level

Frequency/Duration: Single Administration

Response: Never root compression, Transient dysphagia

Patient characteristics (gender, mean age): 54% male, 51.3 years

Number per group: 48 PEEK, 52 silicon nitride

Observations on adverse effects: 9 silicon nitride and 8 PEEK patients had transient dysphagia, with or without hoarseness. One patient in each group had recurrent symptomatic nerve root compression at the index level because of substantial subsidence. In both cases, the device was replaced by an allograft block and the patient had supplemental fixation with a plate and screws.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Farrhokhi et al. 2017[10]

Study Design: RCT

Device or Material: PEEK cage vs acrylic interbody fusion cage

Contact Duration: 12 months

Dose: Single level

Frequency/Duration: Single administration

Response: Disc herniation, Transient hoarseness

Patient characteristics (gender, mean age): 61.3% female, 46 years

Number per group: 32 PEEK, 32 acrylic

Observations on adverse effects: In the PEEK cage group, 2 patients had disc herniation at the lower level that necessitated ACDF. Transient hoarseness occurred in 2 patients in the PEEK cage group and 1 patient in the acrylic cage group.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Hattou et al. 2017[11]

Study Design: Retrospective cohort study

Device or Material: PEEK cage filled with synthetic bone graft (mostly hydroxyapatite)

Contact Duration: 1 year

Dose: Single level

Frequency/Duration: Single administration

Response: Displacement, Neck pain

Patient characteristics (gender, mean age): 80% male, 52 years (range 9 to 88)

Number per group: 34

Observations on adverse effects: PEEK cage displacement occurred in 4 (12%) patients; neck pain in 1 patient.

Timing of adverse effects: <3 months

Factors that predict response: Higher mean age in patients with displacement. Incomplete reduction before fusion may have played a part in secondary displacement.

Source Citation: Liu et al. 2017[12]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cage vs iliac bone graft

Contact Duration: Mean 25 months

Dose: Single level

Frequency/Duration: Single administration

Response: Transient dysphagia, Donor site pain (iliac crest group only)

Patient characteristics (gender, mean age): 56.6% male, 50 years

Number per group: 29 PEEK, 31 iliac bone

Observations on adverse effects: Two patients (6.8%) who received local bone grafts and 9 (29.0%) who received iliac bone grafts suffered perioperative complications, which was significantly higher in the iliac bone graft group ($p = 0.04$). Of these, 2 within the local bone group and 1 from the iliac bone group suffered dysphagia. All recovered spontaneously within 2 weeks. Six patients in the iliac bone group had bone donor site pain, which disappeared at the time of the latest follow-up.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Yson et al. 2017[13]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cage vs structural allograft

Contact Duration: 6 months

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 58.2% female, 50 years

Number per group: 48 PEEK, 19 allograft

Observations on adverse effects: There was no statistically significant difference between subsidence rates of the PEEK (29%; 25/85) and allograft group (28%; 9/32) ($p = 0.69$).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Chen et al. 2016[14]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK self-locking cage (ROI-C or ROI-MC+) vs PEEK cage (Cervios) + anterior cervical plate (CSLP)

Contact Duration: 24 months

Dose: 3-level

Frequency/Duration: single administration

Response: Cage Subsidence

Patient characteristics (gender, mean age): 61.1% male, 54.4 years

Number per group: 28 PEEK, 26 PEEK + plate

Observations on adverse effects: Cage subsidence at 3 months occurred in 11/84 segments in group A and 4/78 segments in group B ($p = 0.08$). Another two segments in group A and another one segment in group B subsided at 6 months postoperatively. Only one segment in group A subsided at 12 months postoperatively with no additional subsidence at 24 months. The subsidence rate showed significant difference between groups ($p = 0.043$) at the last follow-up.

Timing of adverse effects: See above

Factors that predict response: NR

Source Citation: Choi et al. 2016[15]

Study Design: Retrospective cohort study

Device or Material: PEEK cage filled with allograft

Contact Duration: 12 months

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Cage migration, cage subsidence, Transient dysphagia

Patient characteristics (gender, mean age): 65.1% male, 53 years

Number per group: 64 single-level (group A), 45 double-level (group B)

Observations on adverse effects: Seven patients (two in group A, five in group B) suffered from transient dysphagia, but none of these patients had this symptom at 1 month postsurgery. One revision surgery was performed because of anterior cage migration in group A. Cage subsidence occurred in nine patients in group A (9/64, 14.1 %) and nine patients in group B (9/45, 20.0 %). The rates of cage subsidence in the two groups were not significantly different ($p = 0.411$).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Li et al. 2016[16]

Study Design: Systematic review

Device or Material: PEEK cage vs. titanium cage

Contact Duration: 1 to 7 years

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Cage subsidence, Wound pain

Patient characteristics (gender, mean age): 55.7% male, 45.7 to 57.6 years across treatment groups

Number per group: 107 PEEK, 128 titanium

Observations on adverse effects: Subsidence was reported in all of the studies among 33 of the 211 patients in the titanium cage group and among 11 of the 184 in the PEEK cage group. There was a significant difference between the two groups (OR = 3.14; 95 % CI: 1.56 to 6.30; $p = 0.001$) favoring PEEK. 1 instance of limb numbness, 1 instance of neuropathic problem, 1 instance of weakness, and 1 instance of subluxation appeared in the titanium cage group, while there was 1 instance of wound pain in the PEEK cage group in the study by Chou. There were also 2 cases of dislocation reported in the titanium cage group by Chen

Timing of adverse effects: NR

Factors that predict response: Subsidence risk was lower for PEEK cages compared to titanium cages

Source Citation: Liu et. al. 2016[17]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cage + plate (Medtronic vs. Anchored spacer (ROI-C)

Contact Duration: Mean 24 months (range 12 to 36 months)

Dose: 3- or 4-level

Frequency/Duration: Single Administration

Response: Dysphagia

Patient characteristics (gender, mean age): 63.3% female, 57 years

Number per group: 32 PEEK, 28 spacer

Observations on adverse effects: Six patients (21.4 %) complained of mild dysphagia 1 month after surgery in the ROI-C group; the dysphagia of five patients disappeared after 3 months. Only one patient had no apparent relief at the last follow-up, and the incidence of dysphagia in the ROI-C group was approximately 3.6 %. 13 (40.6 %) patients complained of dysphagia in the cage-plate group; 7 patients complained of mild dysphagia, and 6 patients complained of moderate dysphagia 1 month after surgery. After conservative treatment, 5 patients recovered after 3 months, and 1 patient recovered after 6 months. However, 7 patients had no apparent relief at the last follow-up, and the incidence of dysphagia in the cage-plate group was approximately 21.9 %. The difference in dysphagia rate between the two groups was statistically significant ($p = 0.037$).

Timing of adverse effects: See above

Factors that predict response: PEEK cage + plate was associated with higher risk of dysphagia than anchored spacer

Source Citation: Shiban et. al. 2016[18]

Study Design: Retrospective cohort study

Device or Material: Stand-alone empty PEEK cages

Contact Duration: 24 months

Dose: 2- to 4-level

Frequency/Duration: Single administration

Response: Adjacent disc disease, Cage subsidence, Symptomatic pseudarthrosis

Patient characteristics (gender, mean age): 52% male, 55 years

Number per group: 265

Observations on adverse effects: Follow-up operations for symptomatic adjacent disc disease and symptomatic pseudarthrosis were needed in 16 (6 %) and four (1.5 %) cases, respectively. Subsidence was observed in 25, 27, and 15% of segments in 1-, 2-, and 3-level surgeries, respectively.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: El-Tantawny 2015[19]

Study Design: Retrospective cohort study

Device or Material: Stand-alone PEEK cages

Contact Duration: 24 months

Dose: 2- to 4- level

Frequency/Duration: Single administration

Response: Subsidence with recurrent arm pain, Transient dysphagia

Patient characteristics (gender, mean age): 57.1% male, 40.5 years

Number per group: 28

Observations on adverse effects: Transient dysphagia occurred in 5 patients, while significant dysphagia occurred in 2 patients without severe distress and was resolved after 4–5 weeks postoperatively. Subsidence was encountered in 7 fusion levels among 5 patients after 4–6 weeks following surgery with no evidence of progression beyond 2 months. 2 of the 5 patients developed recurrent mild–moderate arm pain at 3-month follow-up and had no significant compression in follow up MRI.

Timing of adverse effects: See above

Factors that predict response: NR

Source Citation: Kim et al. 2015[20]

Study Design: Retrospective controlled cohort study

Device or Material: Stand-alone PEEK cage with round tube (Solis) vs trapezoid tube (MC+) filled with Healos

Contact Duration: 2 years

Dose: Single level

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 59% male, 46.1± 11.0 Solis, 54.8±11.5 MC+

Number per group: 18 Solis, 23 MC+

Observations on adverse effects: Subsidence was reported in 28 (68%) patients (78% Solis, 61% M+).

Timing of adverse effects: 24 months

Factors that predict response: Multivariate analysis indicated that cage type and preoperative segmental kyphosis were significant associated with segmental kyphosis at 24 months.

Source Citation: Xie et al. 2015[21]

Study Design: RCT

Device or Material: PEEK interbody cages containing CS/DBM or autogenous iliac cancellous bone (AIB)

Contact Duration: 24 months

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Donor site pain (not related to PEEK cage), Hoarseness

Patient characteristics (gender, mean age): 52.9% male, 55.4 years.

Number per group: 35 CS/DBM, 33 AIB.

Observations on adverse effects: The complication rate was 8.6 % in the CS group and 18.2 % in the AIB group. The complications in the CS/DBM group included 1 case of superficial wound infection and 2 of hoarseness, while the complications in the AIB group included 2 cases of hoarseness, 1 superficial wound infection in donor site and 3 cases of chronic pain or regional numbness in donor site.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Eastlack et al. 2014[22]

Study Design: Prospective cohort study

Device or Material: PEEK cage + plating with Osteocel Plus cellular allograft

Contact Duration: 24 months

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Dysphagia, Early postoperative complications, Residual stenosis, Vertebral body collapse

Patient characteristics (gender, mean age): 51% male, 51 years.

Number per group: 182

Observations on adverse effects: Early postoperative complications included 2 incidents of new radiculopathy, 1 incident of hypotension that resolved with IV fluids, 1 incident of hypertension that resolved with medication, and 2 incidents of postoperative soft-tissue swelling that resolved with medication. Additional procedures were performed to treat vertebral body collapse (n = 1), dysphagia (n = 1), and residual stenosis (n = 1). In addition, 5 patients underwent additional procedures to treat adjacent segment disease.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Kao et al. 2014[23]

Study Design: Retrospective cohort study

Device or Material: PEEK cages filled with autogenous cancellous bone (Fidji Cervical Cage; Abbott/Zimmer)

Contact Duration: 12 months

Dose: Levels: 1-2 (6.2%), 3-4 (37.8%)

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 61% female, 57.1±12.7 years.

Number per group: 82

Observations on adverse effects: Subsidence was detected in 31 (38%) patients.

Timing of adverse effects: Subsidence rates were 2.2% at 1 month, 6.6% at 3 months, 10.4% at 6 months, and 21.4% at 12 months.

Factors that predict response: Multivariate analysis indicated that >2 treatment levels (vs 1-2), treatment at C5-7 (vs C2-5), and relatively oversized cage use were significantly associated with subsidence.

Source Citation: Klingler et al. 2014[24]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cages vs PMMA spacers (Sulcem or Palacos)

Contact Duration: Mean 2.5 years

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Anterior cage dislocation requiring reoperation

Patient characteristics (gender, mean age): 53.3% male, 55 years.

Number per group: PEEK 39, PMMA Sulcem 37, PMMA Palacos 31.

Observations on adverse effects: In the PEEK cage group, one patient experienced recurrent radicular pain and was reoperated 3 months after anterior cervical discectomy because of anterior cage dislocation at level C5/6 and a new soft prolapse at level C6/7. Reoperation was required for 2 patients in PMMA Sulcem group and 1 patient in PMMA Palacos group.

Timing of adverse effects: : 3 months for PEEK, 1 to 2 years for PMMA groups.

Factors that predict response: NR

Source Citation: Mashhadinezhad et al. 2014[25]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cage with hydroxyapatite granules vs PEEK cage with iliac crest autograft

Contact Duration: 12 months

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Delayed cervical hematoma, Dysphonia, Transient dysphagia

Patient characteristics (gender, mean age): 57.2% male, range 28-65 years.

Number per group: Granule 124, iliac 112.

Observations on adverse effects: **:** 1 delayed cervical hematoma and 1 dysphonia in granule group (dysphonia resolved after 4 months). Some patients in both groups had transient dysphagia.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Kasliwal and O'Toole 2013[26]

Study Design: Retrospective cohort study

Device or Material: PEEK cage

Contact Duration: Mean 6.6 months (range 6 to 33 months)

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: C5 palsy, Transient severe dysphagia

Patient characteristics (gender, mean age): 57.1% female, 51 years.

Number per group: 35

Observations on adverse effects: Transient severe dysphagia (3 patients) and unilateral C5 palsy (1 patient) that returned to normal after 6 months.

Timing of adverse effects: See above.

Factors that predict response: NR

Source Citation: Landriel et al. 2013[27]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cervical cages vs iliac crest autografts

Contact Duration: Mean 28 months (range, 6 to 40 months)

Dose: 1, 2, or 3 levels

Frequency/Duration: Single administration

Response: No PEEK-related complications (iliac crest complications only)

Patient characteristics (gender, mean age): 63.3% female, 50.8 years.

Number per group: 30 PEEK, 30 iliac crest autograft.

Observations on adverse effects: No complications in PEEK group, 20% complication rate in iliac crest group. Three patients (15%) developed chronic iliac crest graft donor site pain, and 2 patients (10%) developed a surgical wound infection at the level of the iliac crest, which was treated with surgical toileting and eventually had a favorable outcome. 1 patient (5%) had a broken fixation system screw requiring reoperation.

Timing of adverse effects: NR

Factors that predict response: Iliac crest graft increased risk of complications.

Source Citation: Lu et al. 2013[28]

Study Design: Matched cohort study

Device or Material:

Contact Duration: Mean months followup: 35 BMP, 25 allograft

Dose: ≥2 levels

Frequency/Duration: Single administration

Response: C-5 nerve root palsy, Cervical swelling, CSF leakage, Difficulty swallowing/breathing, Dysphagia, Hematoma, Laryngeal nerve palsies, Seroma, Wound erythema

Patient characteristics (gender, mean age): 55% female, 51 to 55 years.

Number per group: 100 BMP, 50 allografts.

Observations on adverse effects: Overall dysphagia incidence was slightly higher with allograft (44% vs 40%); dysphagia severity significantly higher with BMP (greatest increase in severity with 2–level ACDF). Other complications with rhBMP included 2 hematoma, 2 seroma, 1 CSF leak, 13 difficulty swallowing/breathing, 3 transient recurrent laryngeal nerve palsies, 1 transient C-5 nerve root palsy. Complications in the allograft group included 3 superficial wound erythema/infection, 1 transient C-5 nerve root palsy.

Timing of adverse effects: Seroma drained on day 5. Difficult swallowing/breathing occurred within week 1.

Factors that predict response: 63% of individuals in the allograft cohort exhibiting pseudoarthrosis were smokers.

Source Citation: Park et al. 2013[29]

Study Design: Cohort study

Device or Material: Stand-alone PEEK cage with local autobone graft (Cervios cag-es, Synthes)

Contact Duration: Mean months followup: 12

Dose: Single level

Frequency/Duration: Single administration

Response: Single administration

Patient characteristics (gender, mean age): 52% female, 51.4 years (range 30 to 74).

Number per group: 31

Observations on adverse effects: Subsidence was detected in 7 (22.6%) patients; 2-3 mm in 3 patients, >4 mm in 4 patients.

Timing of adverse effects: NR.

Factors that predict response: aged >60 years.

Source Citation: Park and Roh 2013[30]

Study Design: Retrospective controlled cohort study

Device or Material: Stand-alone PEEK cage (Solis PEEK; Stryker Spine) with PolyBone or iliac bone

Contact Duration: Mean months followup: 30 (range 24 to 39)

Dose: Single level

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 70% male, 59.6 years PolyBone, 52.7 iliac bone.

Number per group: 24 PolyBone, 23 iliac bones.

Observations on adverse effects: Subsidence was greater with PolyBone; differences in mean segmental angle and mean disc height between groups showing a statistically significant difference at 12 months.

Timing of adverse effects: 12 months.

Factors that predict response: NR

Source Citation: Pereira et al. 2013[31]

Study Design: Prospective case series

Device or Material: Stand-alone PEEK cage

Contact Duration: Mean months radiologic follow up: 23 (range 5 to 75)

Dose: Levels: 4 (23%), 3 (77%)

Frequency/Duration: Single administration

Response: Cage settling, Cage subsidence

Patient characteristics (gender, mean age): 53.3% male, 56.7±7.0 years.

Number per group: 30

Observations on adverse effects: Cage settling and significant discrepancy (>4%) between anterior and posterior heights suggestive of subsidence were observed in 4 (13.3%) and 5 (6.7%) patient(s), respectively.

Timing of adverse effects: long-term.

Factors that predict response: NR

Source Citation: Wang et al. 2013[32]

Study Design: Retrospective case series

Device or Material: Stand-alone PEEK cage (MC+, LDR)

Contact Duration: Mean months followup: 43.6 (range 24 to 78)

Dose: 2 noncontiguous levels

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 56% male, 55.6 years (range 41 to 73).

Number per group: 16 with 2 noncontiguous levels of CDDD.

Observations on adverse effects: 3 (9.38%) cages subsided in 2 patients.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Zagra et al. 2013[33]

Study Design: Retrospective controlled cohort study

Device or Material: Stand-alone PEEK cage containing B-tricalcium phosphate vs stand-alone titanium cage with autologous bone graft vs tricortical iliac bone graft

Contact Duration: Mean years followup: 7 (range 5 to 12)

Dose: 2 level (n = 6), 1 level (n = 80)

Frequency/Duration: Single administration

Response: No PEEK-related complications, Subsidence (titanium cage only)

Patient characteristics (gender, mean age): 52% male, 40 years (range 28 to 63).

Number per group: 24 tricortical, 29 titanium, 33 PEEK.

Observations on adverse effects: Subsidence and migration of titanium cage into the vertebral body were detected in 7 (35%) patients.

Timing of adverse effects: 1 cage subsidence was noted at 5 years.

Factors that predict response: NR

Source Citation: Ba et al. 2012[34]

Study Design: Retrospective cohort study

Device or Material: Carbon fiber-reinforced PEEK (CFRP) cage with local decompression bone (Bengal, Depuy Spine Inc.).

Contact Duration: 5 to 10 years follow-up

Dose: Single level

Frequency/Duration: Single administration

Response: Dysphagia, Hoarseness

Patient characteristics (gender, mean age): 52% female, 54.8 years (range 36 to 78).

Number per group: 207

Observations on adverse effects: Complications included hoarseness in 2 patients, and dysphagia in 6 patients.

Timing of adverse effects: Hoarseness was immediately post-operative.

Factors that predict response: NR

Source Citation: Sudprasert and Kunakornsawat 2012[35]

Study Design: Retrospective cohort study

Device or Material: PEEK cages packed with bone substitute and aspirated bone marrow (Bengal cervical PEEK; Johnson and Johnson, or Skate cervical PEEK; Biomech-Paonan Biotech Co., Ltd)

Contact Duration: Mean years follow-up: 3 (range 2 to 4)

Dose: 3- and 4-level

Frequency/Duration: Single administration

Response: Dysphagia

Patient characteristics (gender, mean age): 62% male, 57.1 years (range 41 to 80).

Number per group: 16

Observations on adverse effects: Dysphagia was observed in 2 (12%) patients.

Timing of adverse effects: Dysphagia subsided >30 days and at 90 days.

Factors that predict response: NR

Source Citation: Vanek et al. 2012[36]

Study Design: Retrospective cohort study

Device or Material: PEEK (Cornerstone, Medtronic) filled with *B*-tricalcium phosphate and plate vs stand-alone autograft vs autograft and anterior plate

Contact Duration: 2-year follow-up

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Graft collapse

Patient characteristics (gender, mean age): 52% female, 53.2±10.7 years.

Number per group: 29 PEEK plus plate, 28 stand-alone autograft, 18 autograft plus plate.

Observations on adverse effects: Graft collapse was noted with stand-alone autograft. Significant differences in relative height (vs preoperative height) were noted as early as 6th postoperative week favoring PEEK plus plate and autograft plus anterior plate vs stand-alone autograft.

Timing of adverse effects: 6 weeks to 2 years.

Factors that predict response: Lack of anterior plating with stand-alone autograft.

Source Citation: Guo et al. 2011[37]

Study Design: Retrospective cohort study

Device or Material: PEEK cage (DePuy Spine; AO spine) with Titanium mesh

Contact Duration: Mean months follow-up: 37.3±7 (range 24 to 48)

Dose: 3-level

Frequency/Duration: Single administration

Response: C5 palsy, CSF leakage, Hematoma, Mesh subsidence

Patient characteristics (gender, mean age): 66% male, 53.4±9.5 years.

Number per group: 53

Observations on adverse effects: Complications included titanium mesh subsidence in 5 (9.4%) patients; and C5 palsy, CSF leakage, and hematoma in 1 (1.9%) patient each.

Timing of adverse effects: CSF leakage at day 1. Subsidence at 3 months.

Factors that predict response: Old age and pre-existing myelopathy were associated with C5 radiculopathy rate.

Source Citation: Hong and Kawaguchi 2011[38]

Study Design: Retrospective cohort study

Device or Material: PEEK cage (Solis, Stryker) packed with allograft

Contact Duration: Mean months follow-up: 15.6 (range 12 to 26)

Dose: 1-level (8), 2-level (23), 3-level (8)

Frequency/Duration: Single administration

Response: CSF leakage, Mild swallowing discomfort, Subcutaneous hematoma due to obstructed drainage

Patient characteristics (gender, mean age): 56% male, 56.6 years (range 39 to 79).

Number per group: 39

Observations on adverse effects: Complications included CSF leakage (1), mild swallowing discomfort (2), and subcutaneous hematoma due to obstructed drainage (1).

Timing of adverse effects: Hematoma at 2 days postoperatively. CSF leakage and swallowing were recovered at 1 week and <1 month, respectively.

Factors that predict response: NR

Source Citation: Iampreechakul et al. 2011[39]

Study Design: Retrospective cohort study

Device or Material: PEEK cage (Cervios, Mathys Medical) filled with bone fragment

Contact Duration: mean months follow-up: 18 (range 12 to 24)

Dose: 1-level (42), 2-level (25)

Frequency/Duration: Single administration

Response: Cage subsidence, Transient dysphagia

Patient characteristics (gender, mean age): 58% female, 45.7 years (range 29 to 85).

Number per group: 67

Observations on adverse effects: Subsidence was observed in 7 (7.61%) patients. Transient dysphagia in 3 patients.

Timing of adverse effects: Subsidence occurred <6 months postoperatively. Dysphagia <2 weeks.

Factors that predict response: Use of oversized cage due to severe narrowing disc space (3), and wearing cervical collar irregularly (3).

Source Citation: Moon et al. 2011[40]

Study Design: Retrospective cohort study

Device or Material: Stand-alone PEEK cage (Solis, Stryker) with DBM

Contact Duration: Mean months follow-up: 25.5 (range 13 to 60)

Dose: 2-level

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 66% male, 50.8 years (range 31 to 67).

Number per group: 27

Observations on adverse effects: Subsidence rates were high (84.6%).

Timing of adverse effects: 1 week to last follow-up

Factors that predict response: NR

Source Citation: Wilkinson et al. 2011[41]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK (Solis, Stryker) vs allograft plus plating

Contact Duration: Mean months follow-up: 12.5 (range 9 to 15)

Dose: 1-and 2-level

Frequency/Duration: Single administration

Response: Dysphagia

Patient characteristics (gender, mean age): 68% male, 48.2 years PEEK, 49.2 allograft.

Number per group: 13 PEEK, 22 allograft plus plating.

Observations on adverse effects: Complications included mild dysphagia in 4 patients with allograft plus plate, and persistent dysphagia in 1 patient with PEEK.

Timing of adverse effects: Dysphagia with PEEK lasted >1 years.

Factors that predict response: NR

Source Citation: Zhou et al. 2011[42]

Study Design: Retrospective cohort study

Device or Material: Self-locking stand-alone PEEK cages (MC+, LDR)

Contact Duration: Mean months follow-up: 19.8 (range 15 to 27)

Dose: 3-level

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 66% male, 57.2 years (range 43 to 71).

Number per group: 15

Observations on adverse effects: Subsidence occurred in 4 (8.89%) of 45 cages inserted in 3 patients.

Timing of adverse effects: NR

Factors that predict response: older age, and possibly osteoporosis

Source Citation: Zhou et al. 2011[43]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cervical cages vs iliac crest autograft

Contact Duration: PEEK: mean 17.3 months (range 12-30 months)

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: No PEEK-related complications, Donor site pain (iliac crest only

Patient characteristics (gender, mean age): 58% male, 55 years.

Number per group: 40 PEEK, 32 iliac crest graft with anterior plating.

Observations on adverse effects: No major postoperative or late complications for either device; donor site pain occurred in 18.75% of iliac crest graft group.

Timing of adverse effects: 3 months postsurgery for donor site pain in iliac crest group; no patients reported pain at final follow-up.

Factors that predict response: Iliac crest graft associated with donor site pain.

Studies that reported no implant-related complications

Source Citation: Li et al. 2019[44]

Study Design: Retrospective controlled cohort study

Device or Material: Allograft bone plus (PEEK cage vs. titanium mesh cage)

Contact Duration: Mean 45.9 months

Dose: 1-level

Frequency/Duration: Single administration

Response: No PEEK-related complications

Source Citation: Phan et al. 2019[45]

Study Design: Prospective cohort study

Device or Material: Composite titanium/PEEK cage

Contact Duration: Mean 7.9 months

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: No implant-related complications

Source Citation: Zapolska et al. 2019[46]

Study Design: Retrospective cohort study

Device or Material: PEEK cage

Contact Duration: Mean 12 months

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: No PEEK-related complications

Source Citation: Kim et al. 2017[47]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cage vs iliac bone graft

Contact Duration: Mean 25-29 months

Dose: 1-level

Frequency/Duration: Single administration

Response: No complications

Source Citation: Luo et al. 2015[48]

Study Design: Retrospective cohort study

Device or Material: Stand-alone PEEK cage

Contact Duration: Mean 39.6 months

Dose: 2-level

Frequency/Duration: Single administration

Response: No PEEK-related complications

Source Citation: Junaid et al. 2014[49]

Study Design: Case series

Device or Material: PEEK cage

Contact Duration: 12 months

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: No PEEK-related complications

Source Citation: Spallone et al. 2014[50]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK vs mini-invasive iliac crest graft

Contact Duration: Mean 3.8 years

Dose: NR

Frequency/Duration: Single administration

Response: No PEEK-related complications

Source Citation: Chang et al. 2013[51]

Study Design: Retrospective cohort study

Device or Material: PEEK cages (Fidgi cage) filled with a synthetic crystallic semihydrate form of calcium sulfate

Contact Duration: Mean 16.9 months (range 12-30 months)

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: No complications or responses

Source Citation: Dufour et al. 2010[52]

Study Design: Retrospective cohort study

Device or Material: PEEK Optima cervical cage (MC+)

Contact Duration: Mean 31 months (range 12–50 months)

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: No complications or responses

ACDF: anterior cervical discectomy and fusion; CDDD: cervical disk degenerative disease; CSF: cerebrospinal fluid; DBM: demineralized bone matrix; DCI: dynamic cervical implant; NR: not reported; PEEK: polyetheretherketone; RCT: randomized controlled trial; rhBMP-2: recombinant human bone morphogenetic protein–2

Table 9: Intervertebral Fusion Device with Bone Graft, Lumbar – Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Hasegawa et al. 2020[53]

Study Design: RCT

Device or Material: PEEK cage vs titanium-coated PEEK cage (TiPEEK)

Contact Duration: 12 months

Dose: Single level

Frequency/Duration: Single administration

Response: Cage Subsidence

Patient characteristics (gender, mean age): 56% male, 67 years

Number per group: 69 and 80

Observed adverse effects: Cage subsidence did not differ between the two cages at any time point (15.6% vs 14.9% at 12 months).

Timing of adverse effects: NA

Factors that predict response: NA

Source Citation: Manabe et al. 2019[54]

Study Design: Retrospective cohort study

Device or Material: Ti-coated PEEK cage

Contact Duration: 12 month minimum followup

Dose: 1-level

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 71% female. 70.6 years

Number per group: 21 (26 spaces)

Observed adverse effects: Subsidence occurred in 5 (19.2%) intervertebral spaces. Mean subsidence was 2.58 mm at 1 year.

Timing of adverse effects: 1 year

Factors that predict response: NR

Source Citation: Wu et al. 2019[55]

Study Design: Controlled cohort study

Device or Material: PEEK cage vs Biocage

Contact Duration: Average 32 months

Dose: Single level

Frequency/Duration: Single administration

Response: Cage rupture, Cage subsidence

Patient characteristics (gender, mean age): 44% male, 55 years

Number per group: 206 and 173

Observed adverse effects: Cage subsidence occurred in 4 patients in the Biocage group and 3 patients in the PEEK group, and cage rupture occurred in 1 patient in the Biocage group

Timing of adverse effects: NA

Factors that predict response: NA

Source Citation: Heinz von der Hoeh et al. 2018[56]

Study Design: Retrospective controlled cohort study

Device or Material: Oblique cage (Mectalif Ti-PEEK, Medacta)

Contact Duration: 24 months followup

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 2:5 to 1 ratio male to female. 67.9±9.4 years.

Number per group: 84

Observed adverse effects: Subsidence occurred in 5 segments (5.7%) in 4 patients; >4 mm (1) and >2 mm (4).

Timing of adverse effects: 24 months

Factors that predict response: age older than 70 years, possible poor quality

Source Citation: Hoppe et al. 2018[57]

Study Design: Case series

Device or Material: Ti-coated carbon PEEK cage (ETurn cage, Icotec)

Contact Duration: Average 29 months

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Unclear whether PEEK-related: Seroma, hematoma, paresthesia, motor deficit, lung embolism, hyposensibility, wound disorder

Patient characteristics (gender, mean age): 55% male, 60 years

Number per group: 42

Observed adverse effects: Seroma 3%, hematoma 3%, paresthesia 10%, motor deficit 7%, lung embolism 3%, hyposensibility 3%, wound disorder 3%.

Timing of adverse effects: 3-11 days postoperative

Factors that predict response: NR

Source Citation: Norotte et al. 2018[58]

Study Design: Case series

Device or Material: Kili cages (Spineway, Lyon, France) made of PEEK-OPTIMA polymer (Invibio).

Contact Duration: 24 months

Dose: Single level

Frequency/Duration: Single administration

Response: Bladder dysfunction, Cage subsidence

Patient characteristics (gender, mean age): 55% male, 48 years

Number per group: 65

Observed adverse effects: 6 patients (9%) had bladder dysfunction; authors did not report whether these were PEEK-related. Cage subsidence (>3 mm collapse) was detected in 4 cases (6.2%) and was related to cage size (more than 11 mm height; $P < 0.05$)

Timing of adverse effects: Postoperative (NR Specifics)

Factors that predict response: Cage size predicted subsidence

Source Citation: Lee et al. 2017[59]

Study Design: Controlled cohort study

Device or Material: PLIF procedure with PEEK cage, vs ALIF with Synfix cage or TLIF with CAPSTONE cage

Contact Duration: 2 years

Dose: Single level

Frequency/Duration: Single administration

Response: Cage subsidence, Persistent postoperative fever, Persistent radiating pain

Patient characteristics (gender, mean age): 79% female, 56 years

Number per group: 26 (ALIF with Synfix cage), 21 (TLIF with CAPTSTONE cage) and 30 (PLIF with PEEK cage)

Observed adverse effects: Unclear whether PEEK-related: PLIF with PEEK cages had 1 case of persistent postoperative fever (1/30) and 1 case of persistent radiating pain (1/30). The two non-PEEK procedures (ALIF and TLIF, data combined) had 1 case of persistent postoperative fever (1/47), 1 case of persistent radiating pain (1/47), 1 case of ileus (1/47), and 1 case of recurrent low back pain (1/47). At 1 year after surgery, the cage subsidence rate was 7.7% in the ALIF group, 33.3% in the TLIF group, and 10% in the PLIF group, with no significant differences between groups ($p = 0.060$). At 2 years after surgery, the cage subsidence rate was 15.4% in the ALIF group, 38.1% in the TLIF group, and 10% in the PLIF group, a significant difference between groups ($p = 0.037$).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Mi et al. 2017[60]

Study Design: Retrospective case-controlled study

Device or Material: PEEK z-cage

Contact Duration: 6 months minimum follow-up

Dose: 1-level

Frequency/Duration: Single administration

Response: Case subsidence

Patient characteristics (gender, mean age): 55% male, 53 years

Number per group: 18

Observed adverse effects: Subsidence occurred in 18 patients

Timing of adverse effects: Cases were enrolled based on occurrence of subsidence

Factors that predict response: Lower preoperative HU values (to assess bone quality) at the global lumbar vertebral body.

Source Citation: Oh et al. 2017[61]

Study Design: Retrospective cohort study

Device or Material: PEEK O.I.C. cages (Stryker)

Contact Duration: Means years follow-up: 4.1 years (range 1.4 to 7.7)

Dose: 1-level

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 63% female, 65.2±8.6 years

Number per group: 102 (139 segments)

Observed adverse effects: Subsidence >1 mm and >3 mm occurred in 82 (59%) segments and 22 (15.8%) segments, respectively.

Timing of adverse effects: 1 year postoperatively

Factors that predict response: Severe osteoporosis was significantly associated with subsidence >3 mm.

Source Citation: Wang et al. 2017[62]

Study Design: Controlled cohort study

Device or Material: PEEK cage (Stryker) plus autograft vs autograft

Contact Duration: Average 40 months

Dose: Single level

Frequency/Duration: Single administration

Response: Cage sagging

Patient characteristics (gender, mean age): 54% female, 43 years.

Number per group: 44 (nonPEEK) and 40 (PEEK)

Observed adverse effects: Smaller (non-significant) loss in disc height with PEEK.

Timing of adverse effects: Decrease in intervertebral space height started at 6 months in both groups.

Factors that predict response: Cage sagging and becoming embedded in bone endplate.

Source Citation: von Wrangel et al. 2017[63]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cage vs Ti cage

Contact Duration: Mean 39±13 months

Dose: Single level

Frequency/Duration: Single administration

Response: Screw loosening and breakage, Adjacent segment degeneration

Patient characteristics (gender, mean age): 57.5% female, 66±12 years.

Number per group: 40 (45 levels).

Observed adverse effects: Screw loosening was observed in two patients (5%) and screw breakage in two patients (5%). All cases of screw loosening and breakage were observed in the PEEK cage group. Adjacent segment degeneration was observed in 3 patients (7.5%), 2 in the PEEK cage group, and 1 in the titanium cage group.

Timing of adverse effects: NA

Factors that predict response: NA

Source Citation: Deng et al. 2016[64]

Study Design: Controlled cohort study

Device or Material: PEEK cage (Shandong We-go Orthopedic Group Medical Polymer Co., Ltd) vs n-HA/PA66 (University- designed)

Contact Duration: Average 24 months

Dose: 1-level (197), 2-level (67), and 3-level (2)

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 54% female, 53 years.

Number per group: 142 PEEK, 124 n-HA/PA66.

Observed adverse effects: Cage subsidence was lower with PEEK at 3 months (2.25%, 3.77%), 6 months (3.37%, 5.66%), and 1 year (5.62%, 6.92%), but higher with PEEK at final followup (8.99%, 7.55%; differences not statistically significant).

Timing of adverse effects: 3 months to 47 months**.**

Factors that predict response: NR

Source Citation: Kuang et al. 2016[65]

Study Design: Case series

Device or Material: PEEK cage (ROI-A Oblique, LDR Medical)

Contact Duration: Average 25 months

Dose: Single and multiple levels

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 59% female, 55 years

Number per group: 22

Observed adverse effects: Cage subsidence was detected in 4 (18.2%) patients in 4 operated levels.

Timing of adverse effects: <6 months

Factors that predict response: NR

Source Citation: Mobbs et al. 2016[66]

Study Design: Case series

Device or Material: Ti/PEEK ALIF cage (A-Spine Asia) with allograft and BMP-2

Contact Duration: Minimum 10 months

Dose: 1-, 2-, and 3-level

Frequency/Duration: Single administration

Response: Cage subsidence, Erectile dysfunction, Ileus

Patient characteristics (gender, mean age): 60% male, 54 years

Number per group: 16

Observed adverse effects: Subsidence ≥2 mm was observed in 3 implants.

Timing of adverse effects: Unclear whether erectile dysfunction (1 patient), and ileus (2 patients) were PEEK-related.

Factors that predict response: NR

Source Citation: Schimmel et al. 2016[67]

Study Design: Case series

Device or Material: Stand-alone PEEK cage (Synfix-LR, Synthes)

Contact Duration: Average 48 months

Dose: 1-level (74), 2-level (21)

Frequency/Duration: Single administration

Response: Unclear whether PEEK-related: retrograde ejaculation, abdominal hematoma, neuroma

Patient characteristics (gender, mean age): 57% female, 43 years

Number per group: 95

Observations on adverse effects: Unclear whether PEEK-related: 1 retrograde ejaculation, 1 abdominal hematoma and 1 neuroma.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Ni et al. 2015[68]

Study Design: Case series

Device or Material: PEEK cage (Synfix-LR PEEK, Synthes; Chesapeake PEEK, K2M; Globus PEEK, Globus Medical)

Contact Duration: Average 28 months

Dose: Single level

Frequency/Duration: Single administration

Response: Cage migration, Cage subsidence

Patient characteristics (gender, mean age): 88% female, 67 years.

Number per group: 40

Observations on adverse effects: Cage subsidence was detected in 8.3% (7/84) of levels. Mild forward cage migration was detected with mean migration distance at final followup by level: 0.83 mm in L3/4, 0.36 mm in L4/5, 0.55 mm in L5/S1.

Timing of adverse effects: Subsidence at 3 months (1.2%) and final follow-up (8.3%).

Factors that predict response: Locally harvested bone and additional posterior fusion.

Source Citation: Allain et al. 2014[69]

Study Design: Case series

Device or Material: PEEK cage (ROI-A, LDR Medical)

Contact Duration: 12 months

Dose: 1-level

Frequency/Duration: Single administration

Response: Single administration

Patient characteristics (gender, mean age): 75% female, 57 years.

Number per group: 65

Observations on adverse effects: Cage migration and cage subsidence occurred in 1 patient each.

Timing of adverse effects: 12-month follow-up

Factors that predict response: Subsidence occurred in a 76-year old female.

Source Citation: Flouzat-Lachaniette et al. 2014[70]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK ROI-A cages (LDR Medical) with either autologous iliac crest bone graft (ICBG) or 6 mg rhBMP-2

Contact Duration: 1 year follow-up

Dose: Levels: 1 (78.4%) and 2 (21.6%)

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 73% female, 59±12 years.

Number per group: 51 (62 levels).

Observations on adverse effects: Cage subsidence was observed in 11 (17.7%) patients.

Timing of adverse effects: 1 year postoperatively

Factors that predict response: NR

Source Citation: Malham et al. 2014[71]

Study Design: Prospective cohort study

Device or Material: PEEK cage (Perimeter, Medtronic) filled with rhBMP-2

Contact Duration: Median 12 months (range 6 to 24)

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Unclear whether PEEK-related: Minor complications: small bowel ileus, atelectasis, hematoma; Major complications: pleural effusion, aspiration pneumonia, DVT

Patient characteristics (gender, mean age): 51% male, 45 years.

Number per group: 131

Observations on adverse effects: Unclear whether PEEK-related: small bowel ileus (4), atelectasis (3), hematoma (2), pleural effusion (2), aspiration pneumonia (1), DVT (1).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Nemoto et al. 2014[72]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK vs Ti (both CAPSTONE cages, Medtronic)

Contact Duration: 24 months follow-up

Dose: 1-level

Frequency/Duration: Single administration

Response: Cage subsidence, Vertebral osteolysis

Patient characteristics (gender, mean age): 94% male. 41.5 years (range 24 to 62).

Number per group: 25 PEEK, 23 Ti.

Observations on adverse effects: At 24 months follow-up, cage subsidence was lower with PEEK vs Ti (28% vs 35%). No significant difference was reported in mean subsidence (1.0±1.8 mm PEEK, 1.1±1.6 mm Ti). However, vertebral osteolysis was detected only on CT in 15 (60%) patients using PEEK (mild (<5 mm) in 6 cases, moderate (5-9 mm) in 9 cases).

Timing of adverse effects: Osteolysis at 12 months persisted at 24 months.

Factors that predict response: NR

Source Citation: Behrbalk et al. 2013[73]

Study Design: Retrospective controlled cohort study

Device or Material: Stand-alone PEEK (SynFix-LR, Synthes)

Contact Duration: Mean months follow-up: 17±6

Dose: Levels: 1 (72%) and 2 (28%)

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 72% female, 52±14 years.

Number per group: 25

Observations on adverse effects: Cage subsidence occurred in 5 (20%) patients.

Timing of adverse effects: 2 subsidence cases: <6 months.

Factors that predict response: Older age, higher BMI.

Source Citation: Jiya et al. 2011[74]

Study Design: RCT

Device or Material: PEEK vs PLDLLA

Contact Duration: 12-month follow-up

Dose: 1-level

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 73% female, 44 years PEEK, 53 PLDLLA.

Number per group: 14 PEEK, 12 PLDLLA.

Observations on adverse effects: A significantly higher rate of subsidence with PLDLLA ($p = 0.04$).

Timing of adverse effects: 1 case of subsidence with PEEK at 1 year.

Factors that predict response: NR

Source Citation: Lee et al. 2011[75]

Study Design: Case series

Device or Material: PEEK (PEEK OIC, Stryker Spine)

Contact Duration: 12-month follow-up

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: Cage subsidence

Patient characteristics (gender, mean age): 57% female, 63 years (37 to 73).

Number per group: 30 (49 segments).

Observations on adverse effects: At 6 months, the levels of subsidence of the vertebral end plate of the upper and lower surface of the cage was 1.65±1.96 mm and 1.32±1.43 mm, respectively. At 12 months, the levels of subsidence of the vertebral end plate of the upper and lower surface of the cage was 1.75±1.68 and 1.34±1.40, respectively.

Timing of adverse effects: 6 months, 12 months.

Factors that predict response: NR

Source Citation: Sethi et al. 2011[76]

Study Design: Controlled cohort study

Device or Material: rhBMP-2 and PEEK vs allograft bone

Contact Duration: 24 months follow-up

Dose: Single and multiple

Frequency/Duration: Single administration

Response: Cage migration, Cage subsidence

Patient characteristics (gender, mean age): 55% male, 51 years (range 18 to 79).

Number per group: 59 PEEK (82 levels), 36 allograft bone (55 levels); 61 lumbar fusion, 34 cervical fusion.

Observations on adverse effects: Subsidence was detected on >50% of all patients at 3 months postoperative. Cage migration occurred in 10 of 26 patients undergoing TLIF with PEEK; incidence significantly higher with PEEK vs allograft for TLIF.

Timing of adverse effects: 6 weeks to 3 months.

Factors that predict response: NR

Studies that reported no implant-related complications

Source Citation: Akbary et al. 2019[77]

Study Design: Case series

Device or Material: PEEK cage (Clydesdale)

Contact Duration: Average 21 months

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: No PEEK-related adverse effects

Source Citation: Novak et al. 2019[78]

Study Design: Case series

Device or Material: PEEK cage (Boomerang, Medtronic)

Contact Duration: 26 months

Dose: 1-level

Frequency/Duration: Single administration

Response: No PEEK-related adverse effects

Source Citation: Rickert et al. 2017[79]

Study Design: RCT

Device or Material: PEEK cage vs TiPEEK (MectaLIF TLIF cage (Medacta International SA)

Contact Duration: 12 months

Dose: 1- and 2-level

Frequency/Duration: Single administration

Response: No PEEK-related adverse effects

Source Citation: Sclafani et al. 2017[80]

Study Design: Retrospective cohort study

Device or Material: Ti-coated PEEK cage (Magnum+Stand-Alone No Profile Interbody Spacer System, Spinal Elements, Inc.)

Contact Duration: Average 9 months

Dose: 1-level (55%), multiple-level (46%)

Frequency/Duration: Single administration

Response: No PEEK-related adverse effects

Source Citation: Sembrano et al. 2017[81]

Study Design: Retrospective controlled cohort study

Device or Material: PEEK cage (lordotic vs non-lordotic)

Contact Duration: NR

Dose: 1-level (23), 2-level (14), 3-level (2), 4-level (1)

Frequency/Duration: Single administration

Response: No PEEK-related adverse effects

Source Citation: Struwe et al. 2017[82]

Study Design: Case series

Device or Material: TWIST PEEK PLIF cage (Twist Technologies)

Contact Duration: 3 years

Dose: NR

Frequency/Duration: Single administration

Response: No PEEK-related adverse effects

Source Citation: Yang et al. 2017[83]

Study Design: Case series

Device or Material: PEEK cage with autograft

Contact Duration: Average 5 years

Dose: Single level

Frequency/Duration: Single administration

Response: No PEEK-related adverse effects

Source Citation: Lin et al. 2016[84]

Study Design: RCT

Device or Material: PEEK cage vs ACSP

Contact Duration: Minimum 2 years

Dose: Single level

Frequency/Duration: Single administration

Response: No PEEK-related adverse effects

Source Citation: Shiban et al. 2016[85]

Study Design: Retrospective cohort study

Device or Material: PEEK cage

Contact Duration: Minimum 12 months

Dose: Single and multiple levels

Frequency/Duration: Single administration

Response: No PEEK-related adverse effects

Source Citation: Lee et al. 2015[86]

Study Design: Retrospective case-control study

Device or Material: PEEK OIC cage (Stryker)

Contact Duration: 1 year

Dose: Single level

Frequency/Duration: Single administration

Response: No PEEK-related adverse effects

Source Citation: Malham et al. 2015[87]

Study Design: Prospective cohort

Device or Material: PEEK cage (CoRoent, NuVasive, Inc.)

Contact Duration: Mean 22.7 months (range 12 to 36)

Dose: 1-level (67.2%), 2-level (27%), 3-level (5.7%)

Frequency/Duration: Single administration

Response: No PEEK-related adverse effects

ACSP: autologous cage using lumbar spinous process and laminae; ALIF: anterior lumbar interbody fusion; BMI: body mass index; DVT: deep vein thrombosis; HU: Hounsfield units; mm: millimeter; n-HA/PA66: nanohydroxyapatite/polyamide66; NA: not applicable; NR: not reported; PEEK: polyetheretherketone; PLIF: posterior lumbar interbody fusion; PLDLLA: poly(L-lactide-co-D,L-lactide); RCT: randomized controlled trial; rhBMP-2: recombinant human bone morphogenic protein 2; Ti: titanium; TLIF: transforaminal lumbar interbody fusion

Table 10: Cranioplasty Plate – Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Liu et al. 2020[88]

Study Design: Systematic review

Device or Material: PEEK, Ti

Contact Duration: Mean months follow-up: 35.4 – 43.2

Dose: NR

Frequency/Duration: Single administration

Response: CSF leak, Exposure, Hematoma, Seizures, Subgaleal effusion

Patient characteristics (gender, mean age): NR, range 30.25 to 43.2 years.

Number per group: 128 PEEK, 238 Ti

Observations on adverse effects: Versus Ti, use of PEEK resulted in significantly lower overall complication rates and implant exposure rates. Rates for hematoma (3.9% PEEK, 3.8% Ti) were similar, while rates of subgaleal effusion (4.7%, 5.0%), CSF (0%, 0.4%), and seizures (4.7%, 9.2%) were lower with PEEK.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Asencio-Cortés et al. 2019[89]

Study Design: Case series

Device or Material: PEEK

Contact Duration: Mean year follow-up: 1 max 5.7 years

Dose: Craniotomy size (cm^2): 6 to 82.45

Frequency/Duration: Single administration

Response: Ulcer

Patient characteristics (gender, mean age): 55% female, 56.01±20.2 years.

Number per group: 60

Observations on adverse effects: Complications were limited to one ulcer.

Timing of adverse effects: 118 days post-implant

Factors that predict response: older age

Source Citation: Bianchi et al. 2019[90]

Study Design: Case series

Device or Material: PEEK

Contact Duration: Mean months follow-up: 20.3±16.4

Dose: Mean dimension (mm): 73.9±24.8 x 69.2 x 16.2

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): 83% female, 54±10.8 years

Number per group: 6

Observations on adverse effects: No implant-related complications were reported

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Morselli et al. 2019[91]

Study Design: Systematic review

Device or Material: PEEK, PMMA, Ti, HA

Contact Duration: Mean 6 to 24 months in PEEK studies

Dose: NR

Frequency/Duration: Single administration

Response: Complication rate, Graft fracture, Graft displacement

Patient characteristics (gender, mean age): ...

Number per group: 233 PEEK (13.82%), 649 Ti (38.49%), 298 PMMA (17.56%), and 508 HA (30.13%).

Observations on adverse effects: Overall complication rates did not differ significantly among different implants: 49 PEEK (21%), 139 Ti (21.4%), 57 PMMA (19.3%), and 103 HA (20.3%). No patients in PEEK group had graft fracture, 2 in Ti group, 1 in PMMA group, and 18 (3.5%) in HA group. 7 cases required revision surgery. Prosthesis displacement occurred in 34 cases (2.02%) and 16 underwent revision surgery (0.95%). All types of displacements were considered. Two cases (0.31%) were recorded in the Ti group, 1 (0.15%) of them required surgical revision; all 11 patients (3.72%) in the PMMA group required revision surgery, 3 patients (1.29%) of the PEEK group with prosthesis mobilization did not require surgical revision, and 4 (0.8%) of the 18 (3.54%) displaced HA prosthesis required a second surgery.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Oliver et al. 2019[92]

Study Design: Systematic review

Device or Material: PEEK, PMMA, Norian, Ti

Contact Duration: Mean months follow-up: 26.8 to 41.0

Dose: NR

Frequency/Duration: Single administration

Response: Complication rate

Patient characteristics (gender, mean age): 72% male overall, 40.1 years overall.

Number per group: 221 PEEK, 1459 PMMA, 1429 Ti, 48 Norian.

Observations on adverse effects: PEEK was associated with a significantly higher rate of local complications vs other implant types (17.19% PEEK, 13.09% Ti, 12.45% Norian, 11.31% PMMA).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Nguyen et al. 2018[93]

Study Design: Cohort

Device or Material: PEEK, PMMA, Ti

Contact Duration: Mean months follow-up: 30

Dose: Defect size (cm^2): 88 to 116 cm^2

Frequency/Duration: Single administration

Response: Dehiscence, Dural tear, Headache, Seroma

Patient characteristics (gender, mean age): 51% male, 11.5 years.

Number per group: 72 PEEK, 42 PMMA, 22 Ti.

Observations on adverse effects: Complications from PEEK included 5.6% dural tear, 4.2% headache, 2.8% seroma, 0% dehiscence. Rates of dural tear were significantly higher with PMMA (21.4% PMMA, 9.1% Ti, 5.6% PEEK).

Timing of adverse effects: NR

Factors that predict response: Age, onlay position

Source Citation: van de Vijfeijken et al. 2018[94]

Study Design: Systematic review

Device or Material: PEEK, autologous bone, PMMA, Ti, HA

Contact Duration: Mean follow-up with PEEK: >1 year

Dose: Defect size (cm^2): mean 100±48.2 (range 1.5 to 517.43)

Frequency/Duration: Single administration

Response: CSF leak, Death, Epilepsy, Exposure, Hematoma, Migration, Overall complication rate, Second trauma, Seizures, Seroma, Wound problems

Patient characteristics (gender, mean age): 60% male, 36.0 years

Number per group: 250 PEEK, 3,335 autologous bone, 1,664 PMMA, 1,829 Ti, 905 HA.

Observations on adverse effects: Overall complication rates (%) highest to lowest were: 35.7 autologous, 22.0 Ti, 21.3 PEEK, 16.8 PMMA, 10.5 HA. Rates for complications with PEEK included: 4.0% hematoma, 0.7% seroma, 0.1% second trauma, 1.3% wound problems, 0.6% exposure, 0% migration, 0% bone resorption, 1.3% CSF leak, 0.4% epilepsy, 2.6% seizures, 0 deaths.

Timing of adverse effects: Immediately postoperative to 9 years.

Factors that predict response: Tissue composition of implants.

Source Citation: Zhang et al. 2018[95]

Study Design: Cohort

Device or Material: PEEK, Ti

Contact Duration: Mean months follow-up: 13.5±4.9 PEEK, 14.2±6.9 Ti

Dose: NR

Frequency/Duration: Single administration

Response: Exposure, Hematoma, New seizures, Subgaleal effusion

Patient characteristics (gender, mean age): PEEK: 82.7% male, 33.27±14.3 years.

Number per group: 75 PEEK, 110 Ti.

Observations on adverse effects: Lower rates of new seizures (4% PEEK, 18.2% Ti, significant difference), implant exposure (1.3%, 9.1%; significant difference), subgaleal effusion (8%, 10.9%) and hematoma (4%, 7.3%) with PEEK.

Timing of adverse effects: NR

Factors that predict response: PEEK implants are embedded and overlap the skull edge in a spatial form.

Source Citation: Brandicourt et al. 2017[96]

Study Design: Case series

Device or Material: PEEK

Contact Duration: Mean years follow-up: 4.3 max 9 years

Dose: NR

Frequency/Duration: Single administration

Response: Subcutaneous hematoma

Patient characteristics (gender, mean age): 60% male, 40±15 years.

Number per group: 37

Observations on adverse effects: 3 subcutaneous hematomas occurred.

Timing of adverse effects: Immediately postoperative.

Factors that predict response: NR

Source Citation: Mrad et al. 2017[97]

Study Design: Case control

Device or Material: PEEK, autogenous

Contact Duration: Minimum follow-up: 1 year

Dose: NR

Frequency/Duration: Single administration

Response: None detected

Patient characteristics (gender, mean age): PEEK: 55% male, 45 years.

Number per group: 9 PEEK, 10 autogenous.

Observations on adverse effects: No complications were detected.

Timing of adverse effects: n/a

Factors that predict response: n/a

Source Citation: Punchak et al. 2017[98]

Study Design: Systematic review

Device or Material: PEEK, Ti, autologous bone

Contact Duration: Mean months follow-up: 24.1

Dose: NR

Frequency/Duration: Single administration

Response: CSF leak, Exposure, Hematoma, New seizures, Overall complications, post-op edema, Seroma, Wound breakdown

Patient characteristics (gender, mean age): 59% male. 38.1 years.

Number per group: 183 PEEK

Observations on adverse effects: Complication rates with PEEK included 2.2% hematoma, 1.6% exposure, 1.1% seroma, 1.1% wound breakdown, 1.1% new seizures, 1.1% CSF leak, and 1.1% post-op edema. No significant differences were reported for overall complications with PEEK vs. Ti or autologous bone graft cranioplasties

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Jonkergouw et al. 2016[99]

Study Design: Cohort

Device or Material: PEEK

Contact Duration: Median months follow-up: 19.1 (IQR 12.5 to 30.6)

Dose: Defect size (cm^2): 106.3±46.1; range 11 to 181

Frequency/Duration: Single administration

Response: CSF leakage, Hematoma, Wound-related problems

Patient characteristics (gender, mean age): 61% male, 43.2±18.1 years.

Number per group: 38 (40 implants).

Observations on adverse effects: 38 (40 implants). ***Observations on adverse effects:*** 11 patients with 11 complications including hematoma (10%), CSF leakage (2.5%), and wound-related problems (2.5%).

Timing of adverse effects: Median time to complications was 35 days (IQR 4.5 to 90.5).

Factors that predict response: Increased likelihood of complications with vascular comorbidity and smoking. Decreased likelihood of complications with tumor.

Source Citation: Liang et al. 2016[100]

Study Design: Cohort

Device or Material: PEEK, PEEK plus acrylic, acrylic, autologous bone, Ti, Ti plus acrylic

Contact Duration: 3 months follow-up

Dose: NR

Frequency/Duration: Single administration

Response: None detected

Patient characteristics (gender, mean age): 38.6% male, 36.2 years

Number per group: 7 PEEK, 1 acrylic and PEEK, 8 acrylic, 53 autologous bone, 17 Ti, 1 Ti plus acrylic.

Observations on adverse effects: No complications with PEEK. Complication rates for other implants were 7.4% bone, 11% Ti, and 14.2% acrylic.

Timing of adverse effects: n/a

Factors that predict response: n/a

Source Citation: Mundinger et al. 2016[101]

Study Design: Case series

Device or Material: PEEK

Contact Duration: Mean months follow-up: 21.9 (range 2.7 to 80)

Dose: Mean defect size (cm^2): 139 (range 57 to 179)

Frequency/Duration: Single administration

Response: Dehiscence

Patient characteristics (gender, mean age): 83% male. 25.8±11.6 years

Number per group: 6

Observations on adverse effects: Incisional dehiscence occurred in 1 patient

Timing of adverse effects: Early postoperative.

Factors that predict response: NR

Source Citation: Alonso-Rodriguez et al. 2015[102]

Study Design: Case series

Device or Material: PEEK

Contact Duration: Months follow-up: 5 to 72

Dose: NR

Frequency/Duration: Single administration

Response: CSF leak, Exposure, Necrosis, Seroma, Sinus inflammation

Patient characteristics (gender, mean age): 71% female, 42.7 years.

Number per group: 14

Observations on adverse effects: Seroma, CSF leakage, exposure due to cutaneous necrosis, and asymptomatic sinus inflammation occurred in 1 patient each.

Timing of adverse effects: Months follow-up for events: leakage (20), seroma (35), exposure (36), and inflammation (38), but this is the follow-up time for the patients who experienced the event, it does not indicate when these events actually occurred.

Factors that predict response: NR

Source Citation: O'Reilly et al. 2015[103]

Study Design: Case series

Device or Material: PEEK

Contact Duration: Mean months follow-up: 59 (range 24 to 106)

Dose: Mean implant size (cm^2): 208.40 (63 to 517.43)

Frequency/Duration: Single administration

Response: Epidural fluid collection, Exposure, Hydrocephalus, Palpable plate

Patient characteristics (gender, mean age): 63% male, 39.6 (15 to 81) years.

Number per group: 19 (22 cranioplasty).

Observations on adverse effects: Complications included traumatic exposure in 1 patient; and palpable plate, threatened exposure, and epidural fluid collection, and hydrocephalus in another patient.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Thien et al. 2015[104]

Study Design: Cohort

Device or Material: PEEK, Ti

Contact Duration: Mean months follow-up: 16.9±14.4 PEEK, 43.1±35.1

Dose: Mean DC size (cm^2): 80.8±47.5 PEEK, 63.3±28.9 Ti

Frequency/Duration: Single administration

Response: Exposure, Extradural hemorrhage, new seizures

Patient characteristics (gender, mean age): PEEK: 54% male, 35.0±16.0 years.

Number per group: 24 PEEK, 108 Ti.

Observations on adverse effects: No significant difference between implant types for exposure (4.2% PEEK, 13.9% Ti), new seizures (8.3% PEEK, 1.9% Ti), and extradural hemorrhage (4.2% PEEK, 0.9% Ti).

Timing of adverse effects: Exposure with PEEK at 1.6 months. Mean time to exposure with Ti was 33.6 months (0.26 to 83.06 months).

Factors that predict response: Previous deep infection after DC was significantly associated with complications.

Source Citation: Rosenthal et al. 2014[105]

Study Design: Cohort

Device or Material: PEEK

Contact Duration: Mean months follow-up: 24±16

Dose: Large cranial defects

Frequency/Duration: Single administration

Response: Epidural hematoma

Patient characteristics (gender, mean age): 71% male, 35±14 years.

Number per group: 65 (66 cranioplasty).

Observations on adverse effects: Complications included 2 (3%) epidural hematomas.

Timing of adverse effects: NR

Factors that predict response: NR

cm^2: square centimeter; CSF: cerebrospinal fluid; DC: decompressive craniectomy; HA: hydroxyapatite; IQR: interquartile range; mm: millimeter; n/a: not applicable; NR: not reported; PEEK: polyether ether ketone; PMMA: polymethyl methacrylate; Ti: titanium

Table 11: Plate, Fixation, Bone – Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Cofano et al. 2020[106]

Study Design: Controlled cohort study with historical control group

Device or Material: Plate, fixation, bone

Contact Duration: Mean follow-up 8 months (CFR-PEEK), 14 months (titanium)

Dose: CFR-PEEK implants (CarboClear, BlackArmor) vs titanium implants (EXPEDIUM, MOUNTAINEER)

Frequency/Duration: Single administration (implant)

Response: Hardware malfunctions (titanium only)

Patient characteristics (gender, mean age): ***):*** CFR-PEEK: 63.9% male, 62.2 years. Titanium: 59.5% male, 65.6 years.

Number per group: 36 CFR-PEEK, 42 titanium.

Observations on adverse effects (brief): 1 screw loosening (2.2%) in titanium group. No other hardware malfunctions in either group.

Timing of adverse effects: Assessments at 3, 6, and 12 months and yearly thereafter.

Factors that predict response: NR

Source Citation: Tarallo et al. 2020[107]

Study Design: Case series

Device or Material: Plate, fixation, bone

Contact Duration: Mean follow-up 4 years

Dose: CFR-PEEK plates (DiPhos-RM)

Frequency/Duration: Single administration (implant)

Response: Extensor tendon irritation

Patient characteristics (gender, mean age): 33 male, 77 female; average age 58 years.

Number per group: 110

Observations on adverse effects (brief): 2 patients experienced extensor tendon irritation.

Timing of adverse effects: 5- and 10-months post-surgery

Factors that predict response: NR

Source Citation: Allemann et al. 2019[108]

Study Design: Case series

Device or Material: Plate, fixation, bone

Contact Duration: 1 year follow-up

Dose: 2.7 mm CFR-PEEK plates (BlackArmor)

Frequency/Duration: Single administration (implant)

Response: No complications

Patient characteristics (gender, mean age): 60% male, 53.3 years

Number per group: 10

Observations on adverse effects (brief): No adverse effects reported.

Timing of adverse effects: Assessments at 6 weeks, 12 weeks, and 1 year postsurgery.

Factors that predict response: NR

Source Citation: Järvinen et al. 2019[109]

Study Design: Case series

Device or Material: Plate, fixation, bone

Contact Duration: Average follow-up 16.2 months

Dose: PEEK patient-specific maxillofacial implants (Planmeca, DePuy Synthes)

Frequency/Duration: Single administration of 1 or more implants

Response: No PEEK-related complications

Patient characteristics (gender, mean age): 15 female, 9 male; 30.8 years.

Number per group: 24

Observations on adverse effects (brief): No PEEK-related complications.

Timing of adverse effects: NA

Factors that predict response: NA

Source Citation: Padolino et al. 2018[110]

Study Design: Controlled cohort study

Device or Material: Plate, fixation, bone

Contact Duration: Mean follow-up 30.7 months (CFR-PEEK), 57.2 months (titanium)

Dose: 4.4 mm CFR-PEEK plates (Diphos H) versus 3.5 mm titanium plates (PHILOS)

Frequency/Duration: Single administration (implant)

Response: Pain, Stress shielding, Poor calcar reduction, Tuberosity resorption, Screw perforation and cutout

Patient characteristics (gender, mean age): CFR-PEEK: 43% male, 57.4 years. Titanium: 33% male, 55.8 years.

Number per group: 21

Observations on adverse effects (brief): Higher pain score in titanium group, but difference not significant. Stress shielding significantly greater in CFR-PEEK group (mean difference, 1.14 mm; p = 0.0003). Poor calcar reduction (grade 3) found in 2 CFR-PEEK patients, but difference between groups not significant. Significantly higher rate of tuberosity resorption in titanium group (p = 0.040); rate of

screw perforation and cutout similar in the two groups (2 in CFR-PEEK group and 3 in titanium group).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Roberson et al. 2018[111]

Study Design: Controlled cohort study with historical control group

Device or Material: Plate, fixation, bone

Contact Duration: Mean follow-up 32 months (PEEK), 47 months (metal)

Dose: PEEK implants (iBalance) versus metal plates (ContourLock, VS Osteotomy plate)

Frequency/Duration: Single administration (implant)

Response: Complex regional pain syndrome, Deep vein thrombosis

Patient characteristics (gender, mean age): PEEK: 76% male, 43 years. Metal: 60% male, 44 years.

Number per group: 21 PEEK, 20 metal.

Observations on adverse effects (brief): 1 patient developed complex regional pain syndrome, and 1 developed deep vein thrombosis (both in PEEK group).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: DiMaggio et al. 2017[112]

Study Design: Case series

Device or Material: Plate, fixation, bone

Contact Duration: 12-month follow-up

Dose: 2.4 mm CFR-PEEK plate (Piccolo)

Frequency/Duration: Single administration (implant)

Response: Hardware malfunctions

Patient characteristics (gender, mean age): 40.6% male, 56.8 years.

Number per group: 64 in analysis.

Observations on adverse effects (brief): 1 case of aseptic loosening; no other hardware malfunctions observed.

Timing of adverse effects:5 months postsurgery.

Factors that predict response: NR

Source Citation: Guzzini et al. 2017[113]

Study Design: Controlled cohort study

Device or Material: Plate, fixation, bone

Contact Duration: Mean follow-up 14 months

Dose: CFR-PEEK plates vs stainless steel plates (manufacturers unknown)

Frequency/Duration: Single administration (implant)

Response: No PEEK-related complications

Patient characteristics (gender, mean age): CFR-PEEK: 30.4% male, mean age 56.8 years. Stainless: 26.8% male, mean age 58.3 years.

Number per group: 46 CFR-PEEK, 41 stainless.

Observations on adverse effects (brief): ***):*** No PEEK-related complications.

Timing of adverse effects: Assessments at 6, 12, and 24 months post-surgery.

Factors that predict response: NA

Source Citation: Katthagen et al. 2017[114]

Study Design: Non-randomized comparison study (matched design using historical control cohort)

Device or Material: Plate, fixation, bone

Contact Duration: 12-month follow-up

Dose: CFR-PEEK plates (PEEKPower) versus titanium plates (PHILOS)

Frequency/Duration: Single administration (implant)

Response: Screw perforations

Patient characteristics (gender, mean age): CFR-PEEK: 33.3% male, 66.8 years. Titanium: 33.3% male, 67.4 years.

Number per group: 21

Observations on adverse effects (brief): ***):*** Patients in titanium group more likely to require revision surgery related to articular screw perforations ($p = 0.048$).

Timing of adverse effects: Assessments at 3 and 12 months postsurgery.

Factors that predict response: NR

Source Citation: Cotic et al. 2015[115]

Study Design: Case series

Device or Material: Plate, fixation, bone

Contact Duration: 24 month follow-up

Dose: CFR-PEEK plates (2nd-gen PEEKPower)

Frequency/Duration: Single administration (implant); removed in 64% of patients at a mean of 17 months

Response: Complications

Patient characteristics (gender, mean age): 67.9% male, 45 years.

Number per group: 28

Observations on adverse effects (brief): Only complication was 1 non-union, for an overall complication rate of 4%.

Timing of adverse effects: Assessments at 12 and 24 months.

Factors that predict response: NR

Source Citation: Schliemann et al. 2015[116]

Study Design: Non-randomized comparison study (matched design using historical control cohort)

Device or Material: Plate, fixation, bone

Contact Duration: 24-month follow-up

Dose: 30% CFR-PEEK plates (DiPhos-H) versus conventional locking plates (manufacturer not specified)

Frequency/Duration: Single administration (implant)

Response: Malalignment, Avascular necrosis

Patient characteristics (gender, mean age): CFR-PEEK: 76% male, mean age 66.4 years. Conventional group: NR (matched to CFR-PEEK on gender and age).

Number per group: 29 (23 CFR-PEEK patients provided 24-month data).

Observations on adverse effects (brief): Malalignment in 14% of CFR-PEEK group and 24% of conventional group. Avascular necrosis in 3% of CFR-PEEK group and 10% of conventional group. No other complications.

Timing of adverse effects: Assessments at 6 weeks, 6 months, 12 months, and 24 months after surgery.

Factors that predict response: NR

Source Citation: Cotic et al. 2015[117]

Study Design: Controlled cohort study

Device or Material: Plate, fixation, bone

Contact Duration: Median follow-up 25 months

Dose: CFR-PEEK plates (1st-gen PEEKPower) versus titanium plates (TomoFix)

Frequency/Duration: Single administration (implant). Removed in 85% of patients at a mean of 17 months

Response: Hardware malfunctions Inflammation (at removal; CFR-PEEK only)

Patient characteristics (gender, mean age): 76% male, 41 years (both groups).

Number per group: 26

Observations on adverse effects (brief): 1 of 26 CFR-PEEK patients experienced screw loosening after a fall; no hardware malfunctions in titanium group. No signs of acute inflammation in any CFR-PEEK patients.

Timing of adverse effects: 4 weeks post-surgery

Factors that predict response: NR

Source Citation: Tarallo et al. 2014[118]

Study Design: Case series

Device or Material: Plate, fixation, bone

Contact Duration: 12-month follow-up

Dose: CFR-PEEK plates (DiPhos-HRM)

Frequency/Duration: Single administration (implant

Response: Extensor tenosynovitis, Loss of screw position or alignment

Patient characteristics (gender, mean age): 40% male, average age 65 years.

Number per group: 40

Observations on adverse effects (brief): In one case, a 55-year-old male, clinical signs of extensor tenosynovitis were reported 6 months after surgery. The diagnosis of extensor tenosynovitis was primarily based on the symptoms of pain, swelling, tenderness, and dorsal crepitus. Radiographs revealed an excessive length of one screw of the distal branch of the plate, after which the plate and the screws were removed.

Timing of adverse effects: 6 months.

Factors that predict response: NR

CFR: carbon fiber reinforced; NA: not applicable; NR: not reported; PEEK: polyether ether ketone

Table 12: Spinal Vertebral Body Replacement – Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Velonakis et al. 2019[119]

Study Design: Case series

Device or Material: Expandable coil PEEK device (KIVA) placed within fractured vertebrae

Contact Duration: 24 months

Dose: 1 implant

Frequency/Duration: Single administration

Response: None, no device-related complications or foreign body reaction

Patient characteristics (gender, mean age): 14 females, 6 males, 73 years.

Number per group: 20

Observations on adverse effects (brief):

Timing of adverse effects:

Factors that predict response:

Source Citation: Korovessis et al. 2018[120]

Study Design: Controlled cohort

Device or Material: Expandable coil PEEK device (KIVA) placed within fractured vertebrae

Contact Duration: 28 months

Dose: 1 KIVA implant in all patients

Frequency/Duration: Single administration

Response: None, no device-related complications or foreign body reaction

Patient characteristics (gender, mean age): 15 women, 4 men, 45.7±8 years (range: 38–53 years) in one group and 15 women, 4 men aged 46±6 years (range: 40–52 years) in another group.

Number per group: 19; 38 total.

Observations on adverse effects (brief): NR

Timing of adverse effects: NA

Factors that predict response: NA

Source Citation: Beall et al. 2017[121]

Study Design: RCT

Device or Material: Expandable coil PEEK device (KIVA) placed within fractured vertebrae

Contact Duration: 12 months

Dose: 1 implant

Frequency/Duration: Single administration

Response: None

Patient characteristics (gender, mean age): Female 105, male 39, 76 years.

Number per group: 144

Observations on adverse effects (brief): No device-related complications or foreign body reaction.

Timing of adverse effects: NA

Factors that predict response: NA

Source Citation: Korovessis et al. 2014[122]

Study Design: Retrospective controlled cohort study

Device or Material: Expandable coil PEEK device (KIVA) placed within fractured vertebrae

Contact Duration: 26 months

Dose: 1 implant

Frequency/Duration: Single administration

Response: None

Patient characteristics (gender, mean age): 19 women, 19 men, 65 years.

Number per group: 18 calcium phosphate, 20 PEEK.

Observations on adverse effects (brief): No significant medical and surgical complications were observed in the patients of both groups.

Timing of adverse effects: NA

Factors that predict response: NA

Source Citation: Raslan et al. 2014[123]

Study Design: Case series

Device or Material: PEEK cervical implant

Contact Duration: 28 ± 12 months

Dose: 18 1-level and 3 2-level

Frequency/Duration: Single administration

Response: CSF leakage, Screw misplacement leading to pain and dysphagia, Subsidence

Patient characteristics (gender, mean age): NR, 65±9 years.

Number per group: 21

Observations on adverse effects (brief): In 4 patients, reoperation was necessary: in 1 patient due to CSF leakage, in another due to screw misplacement in the first operation. In 1 patient, subsidence of the cage and loosening of screws occurred 3 months after 1-level ACCF, caused progressive nuchal pain and was followed by surgical revision. In another case, cage subsidence and displacement of

the lower pair of screws occurred 2 months after 1-level ACCF and was followed by immediate reoperation because of incapacitating neck pain and swallowing difficulties.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Heary et al. 2011[124]

Study Design: Case series

Device or Material: PEEK cages, thoracolumbar

Contact Duration: Mean 43 months

Dose: 1 to 4 levels

Frequency/Duration: 31 one-level, 9 multiple-level

Response: Cage subsidence with worsening kyphosis and back pain

Patient characteristics (gender, mean age): 26 male, 14 female, 41 years.

Number per group: 40

Observations on adverse effects (brief): 1 patient developed cage subsidence with worsening kyphosis and back pain

Timing of adverse effects: Back pain developed at 6 months.

Factors that predict response: NR

ACCF: anterior cervical corpectomy and fusion; CSF: cerebrospinal fluid; NA: not applicable; NR: not reported; PEEK: polyether ether ketone; RCT: randomized controlled trial; Ti: titanium

Table 6. Spinal Pedicle Fixation – Health Effect (*In Vivo*) Human Studies

Local Response/Toxicity

Source Citation: Koban et al. 2020[125]

Study Design: Retrospective cohort study

Device or Material: PEEK stabilization rods

Contact Duration: 24 months

Dose: Combination screws and rods

Frequency/Duration: Single administration

Response: Screw loosening, adjacent segment disease

Patient characteristics (gender, mean age): 43 female, 15 male, 59 years.

Number per group: PEEK n = 16, titanium n = 42.

Observations on adverse effects (brief): This study reported complications (screw loosening and adjacent segment disease) that required revision surgery in 4/16 patients (25%) receiving dynamic stabilization with PEEK rods. This was a significantly lower rate of revision surgery than that observed for patients receiving rigid stabilization with titanium rods (24/42, 57.1%).

Timing of adverse effects: NR

Factors that predict response: NR

PEEK = polyether ether ketone; NR = not reported

References

1. Ahmed OE, Galal A. Single level anterior cervical discectomy and fusion versus dynamic cervical implant: clinical and radiological outcome. Egypt J Neurol Psychiatry Neurosurg. 2020 Dec;56:26. Also available: http://dx.doi.org/10.1186/s41983-020-0153-0.
2. Ashour AM, Abdelmohsen I, Sawy ME, Toubar AF. Stand-alone polyetheretherketone cages for anterior cervical discectomy and fusion for successive four-level degenerative disc disease without plate fixation. J Craniovertebr Junction Spine. 2020 Apr;11(2):118-23. Also available: http://dx.doi.org/10.4103/jcvjs.JCVJS_62_20.
3. Khattab MF, Kotb A. Cervical stand-alone PEEK cage versus anchored cage with screws in single-level anterior cervical discectomy and fusion: a prospective cohort study. Curr Orthop Pract. 2020;31(2):179-85. Also available: http://dx.doi.org/10.1097/BCO.0000000000000853.
4. Moo IH, Kam CJW, Lai MWS, Yeo W, Soh RCC. A comparison of contiguous two-level anterior cervical discectomy and fusion using a structural allograft versus a Polyetheretherketone (PEEK) cage: the results of a three-year follow-up. BMC Musculoskelet Disord. 2020 May 28;21(1):331. Also available: http://dx.doi.org/10.1186/s12891-020-03325-y. PMID: 32466749.
5. Yang S, Yu Y, Liu X, Zhang Z, Hou T, Xu J, Wu W, Luo F. Clinical and radiological results comparison of allograft and polyetheretherketone cage for one to two-level anterior cervical discectomy and fusion: a CONSORT-compliant article. Medicine (Baltimore). 2019 Nov;98(45):e17935. Also available: http://dx.doi.org/10.1097/MD.0000000000017935. PMID: 31702680.
6. Godlewski B, Stachura MK, Czepko RA, Banach M, Czepko R. Analysis of changes in cervical spinal curvature and intervertebral disk space height following ACDF surgery in a group of 100 patients followed up for 12 months. J Clin Neurosci. 2018 Jun;52:92-9. Also available: http://dx.doi.org/10.1016/j.jocn.2018.04.005. PMID: 29656879.
7. Hu B, Yang X, Hu Y, Lyu Q, Liu L, Zhu C, Zhou C, Song Y. The n-HA/PA66 cage versus the PEEK cage in anterior cervical fusion with single-level discectomy during 7 years of follow-up. World Neurosurg. 2019 Mar;123:e678-e684. Also available: http://dx.doi.org/10.1016/j.wneu.2018.11.251. PMID: 30576825.
8. Junaid M, Rashid MU, Bukhari SS, Ahmed M. Radiological and clinical outcomes in patients undergoing anterior cervical discectomy and fusion: comparing titanium and PEEK (polyetheretherketone) cages. Pak J Med Sci. 2018 Nov;34(6):1412-7. Also available: http://dx.doi.org/10.12669/pjms.346.15833.
9. Arts MP, Wolfs JFC, Corbin TP. Porous silicon nitride spacers versus PEEK cages for anterior cervical discectomy and fusion: clinical and radiological results of a single-blinded randomized controlled trial. Eur Spine J. 2017 Sep;26(9):2372-9. Also available: http://dx.doi.org/10.1007/s00586-017-5079-6. PMID: 28382392.
10. Farrokhi MR, Nikoo Z, Gholami M, Hosseini K. Comparison between acrylic cage and polyetheretherketone (PEEK) cage in single-level anterior cervical discectomy and fusion. Clin Spine Surg. 2017;30(1):38-46. Also available: http://dx.doi.org/10.1097/BSD.0000000000000251. PMID: 28107234.
11. Hattou L, Morandi X, Lefebvre J, Le Reste PJ, Riffaud L, Hénaux PL. Anterior cervical interbody fusion using polyetheretherketone cage filled with synthetic bone graft in acute cervical spine injury. Orthop Traumatol Surg Res. 2017 Feb;103(1):61-6. Also available: http://dx.doi.org/10.1016/j.otsr.2016.09.004. PMID: 27720376.
12. Liu JM, Xiong X, Peng AF, Xu M, Chen XY, Long XH, Xu R, Liu ZL. A comparison of local bone graft with PEEK cage versus iliac bone graft used in anterior cervical discectomy and fusion. Clin Neurol Neurosurg. 2017 Apr;155:30-5. Also available: http://dx.doi.org/10.1016/j.clineuro.2017.02.009. PMID: 28242558.
13. Yson SC, Sembrano JN, Santos ERG. Comparison of allograft and polyetheretherketone (PEEK) cage subsidence rates in anterior cervical discectomy and fusion (ACDF). J Clin Neurosci. 2017 Apr;38:118-21. Also available: http://dx.doi.org/10.1016/j.jocn.2016.12.037. PMID: 28153602.

14. Chen Y, Lü G, Wang B, Li L, Kuang L. A comparison of anterior cervical discectomy and fusion (ACDF) using self-locking stand-alone polyetheretherketone (PEEK) cage with ACDF using cage and plate in the treatment of three-level cervical degenerative spondylopathy: a retrospective study with 2-year follow-up. Eur Spine J. 2016 Jul;25(7):2255-62. Also available: http://dx.doi.org/10.1007/s00586-016-4391-x. PMID: 26906171.

15. Choi MK, Kim SB, Park CK, Kim SM. Comparison of the clinical and radiologic outcomes obtained with single- versus two-level anterior cervical decompression and fusion using stand-alone PEEK cages filled with allograft. Acta Neurochir (Wien). 2016 Mar;158(3):481-7. Also available: http://dx.doi.org/10.1007/s00701-015-2692-1. PMID: 26758609.

16. Li ZJ, Wang Y, Xu GJ, Tian P. Is PEEK cage better than titanium cage in anterior cervical discectomy and fusion surgery? A meta-analysis. BMC Musculoskelet Disord. 2016 Sep;17(1):379. Also available: http://dx.doi.org/10.1186/s12891-016-1234-1. PMID: 27585553.

17. Liu Y, Wang H, Li X, Chen J, Sun H, Wang G, Yang H, Jiang W. Comparison of a zero-profile anchored spacer (ROI-C) and the polyetheretherketone (PEEK) cages with an anterior plate in anterior cervical discectomy and fusion for multilevel cervical spondylotic myelopathy. Eur Spine J. 2016 Jun;25(6):1881-90. Also available: http://dx.doi.org/10.1007/s00586-016-4500-x. PMID: 26968876.

18. Shiban E, Gapon K, Wostrack M, Meyer B, Lehmberg J. Clinical and radiological outcome after anterior cervical discectomy and fusion with stand-alone empty polyetheretherketone (PEEK) cages. Acta Neurochir (Wien). 2016 Feb;158(2):349-55. Also available: http://dx.doi.org/10.1007/s00701-015-2630-2. PMID: 26620448.

19. El-Tantawy A. Is it possible to eliminate the plate-related problems and still achieve satisfactory outcome after multilevel anterior cervical discectomy? Eur J Orthop Surg Traumatol. 2015 Jul;25(Suppl 1):135-45. Epub 2015 Feb 24. Also available: http://dx.doi.org/10.1007/s00590-015-1611-8. PMID: 25708620.

20. Kim CH, Chung CK, Jahng TA, Park SB, Sohn S, Lee S. Segmental kyphosis after cervical interbody fusion with stand-alone polyetheretherketone (PEEK) cages: a comparative study on 2 different PEEK cages. J Spinal Disord Tech. 2015 Feb;28(1):E17-24. Also available: http://dx.doi.org/10.1097/BSD.0000000000000137. PMID: 25089672.

21. Xie Y, Li H, Yuan J, Fu L, Yang J, Zhang P. A prospective randomized comparison of PEEK cage containing calcium sulphate or demineralized bone matrix with autograft in anterior cervical interbody fusion. Int Orthop. 2015 Nov 30;39(6):1129-36. Also available: http://dx.doi.org/10.1007/s00264-014-2610-9. PMID: 25432324.

22. Eastlack RK, Garfin SR, Brown CR, Meyer SC. Osteocel plus cellular allograft in anterior cervical discectomy and fusion: evaluation of clinical and radiographic outcomes from a prospective multicenter study. Spine (Phila Pa 1976). 2014 Oct 15;39(22):E1331-7. Also available: http://dx.doi.org/10.1097/BRS.0000000000000557. PMID: 25188591.

23. Kao TH, Wu CH, Chou YC, Chen HT, Chen WH, Tsou HK. Risk factors for subsidence in anterior cervical fusion with stand-alone polyetheretherketone (PEEK) cages: a review of 82 cases and 182 levels. Arch Orthop Trauma Surg. 2014 Sep 19;134(10):1343-51. Also available: http://dx.doi.org/10.1007/s00402-014-2047-z. PMID: 25099076.

24. Klingler JH, Krüger MT, Sircar R, Kogias E, Scholz C, Volz F, Scheiwe C, Hubbe U. PEEK cages versus PMMA spacers in anterior cervical discectomy: comparison of fusion, subsidence, sagittal alignment, and clinical outcome with a minimum 1-year follow-up. Sci World J. 2014;2014:398396. Also available: http://dx.doi.org/10.1155/2014/398396. PMID: 25110734.

25. Mashhadinezhad H, Samini F, Zare R. Comparison of outcomes and safety of using hydroxyapatite granules as a substitute for autograft in cervical cages for anterior cervical discectomy and interbody fusion. Arch Bone Jt Surg. 2014 Mar;2(1):37-42. PMID: 25207311.

26. Kasliwal MK, O'Toole JE. Clinical experience using polyetheretherketone (PEEK) intervertebral structural cage for anterior cervical corpectomy and fusion. J Clin Neurosci. 2014 Feb;21(2):217-20. Also available: http://dx.doi.org/10.1016/j.jocn.2013.03.018. PMID: 24018256.

27. Landriel FA, Hem S, Goldschmidt E, Ajler P, Vecchi E, Carrizo A. Polyetheretherketone interbody cages versus autogenous iliac crest bone grafts with anterior fixation for cervical disc disease. J Spinal Disord Tech. 2013 Apr;26(2):61-7.

28. Lu DC, Tumialán LM, Chou D. Multilevel anterior cervical discectomy and fusion with and without rhBMP-2: a comparison of dysphagia rates and outcomes in 150 patients - clinical article. J Neurosurg Spine. 2013 Jan;18(1):43-9. Also available: http://dx.doi.org/10.3171/2012.10.SPINE10231. PMID: 23157278.

29. Park JI, Cho DC, Kim KT, Sung JK. Anterior cervical discectomy and fusion using a stand-alone polyetheretherketone cage packed with local autobone: assessment of bone fusion and subsidence. J Korean Neurosurg Soc. 2013 Sep;54(3):189-93. Also available: http://dx.doi.org/10.3340/jkns.2013.54.3.189.

30. Park JH, Roh SW. Anterior cervical interbody fusion using polyetheretherketone cage filled with autologous and synthetic bone graft substrates for cervical spondylosis: comparative analysis between PolyBone® and iliac bone. Neurol Med Chir (Tokyo). 2013 Feb;53(2):85-90. Also available: http://dx.doi.org/10.2176/nmc.53.85. PMID: 23438658.

31. Pereira EAC, Chari A, Hempenstall J, Leach JCD, Chandran H, Cadoux-Hudson TAD. Anterior cervical discectomy plus intervertebral polyetheretherketone cage fusion over three and four levels without plating is safe and effective long-term. J Clin Neurosci. 2013 Sep;20(9):1250-5. Also available: http://dx.doi.org/10.1016/j.jocn.2012.10.028. PMID: 23890411.

32. Wang HR, Li XL, Dong J, Yuan FL, Zhou J. Skip-level anterior cervical discectomy and fusion with self-locking stand-alone PEEK cages for the treatment of 2 noncontiguous levels of cervical spondylosis. J Spinal Disord Tech. 2013 Oct;26(7):E286-92. Also available: http://dx.doi.org/10.1097/BSD.0b013e31828679b3. PMID: 23381180.

33. Zagra A, Zagra L, Scaramuzzo L, Minoia L, Archetti M, Giudici F. Anterior cervical fusion for radicular-disc conflict performed by three different procedures: clinical and radiographic analysis at long-term follow-up. Eur Spine J. 2013 Nov;22(Suppl 6):S905-9. Epub 2013 Sep 27. Also available: http://dx.doi.org/10.1007/s00586-013-3006-z. PMID: 24072338.

34. Ba Z, Zhao W, Wu D, Shen B, Yu B, Wang Z. Box cages packed with local decompression bone were efficient in anterior cervical discectomy and fusion: five-to 10-year follow-up. Spine (Phila Pa 1976). 2012 Sep 15;37(20):E1260-3. Also available: http://dx.doi.org/10.1097/BRS.0b013e318265df75. PMID: 22744617.

35. Sudprasert W, Kunakornsawat S. A preliminary study of three and four levels degenerative cervical spondylosis treated with peek cages and anterior cervical plate. J Med Assoc Thai. 2012 Jul;95(7):909-16. PMID: 22919986.

36. Vanek P, Bradac O, Delacy P, Saur K, Belsan T, Benes V. Comparison of 3 fusion techniques in the treatment of the degenerative cervical spine disease. Is stand-alone autograft really the "gold standard?": prospective study with 2-year follow-up. Spine (Phila Pa 1976). 2012 Sep;37(19):1645-51. Also available: http://dx.doi.org/10.1097/BRS.0b013e31825413fe. PMID: 22433506.

37. Guo Q, Ni B, Zhou F, Lu X, Yang J, Chen J, Yu Y, Zhu L. Anterior hybrid decompression and segmental fixation for adjacent three-level cervical spondylosis. Arch Orthop Trauma Surg. 2011 May;131(5):631-6. Also available: http://dx.doi.org/10.1007/s00402-010-1181-5. PMID: 20809065.

38. Hong L, Kawaguchi Y. Anterior cervical discectomy and fusion to treat cervical spondylosis with sympathetic symptoms. J Spinal Disord Tech. 2011 Feb;24(1):11-14. Also available: http://dx.doi.org/10.1097/BSD.0b013e3181dd80f5. PMID: 20625322.

39. Iampreechakul P, Srisawat C, Tirakotai W. Stand-alone cervical polyetheretherketone (PEEK) cage (Cervios) for single to two-level degenerative disc disease. J Med Assoc Thai. 2011 Feb;94(2):185-92. PMID: 21534365.

40. Moon HJ, Kim JH, Kim JH, Kwon TH, Chung HS, Park YK. The effects of anterior cervical discectomy and fusion with stand-alone cages at two contiguous levels on cervical alignment and outcomes. Acta Neurochir (Wien). 2011 Mar;153(3):559-65. Also available: http://dx.doi.org/10.1007/s00701-010-0879-z. PMID: 21132445.

41. Wilkinson JS, Mann SA, Stoneham GW, Hentschel S, Fourney DR. Comparison of post-operative lordosis with the PEEK cage and the cervical plate. Can J Neurol Sci. 2011 Jan;38(1):72-7. Also available: http://dx.doi.org/10.1017/S0317167100011100. PMID: 21156433.

42. Zhou J, Li X, Dong J, Zhou X, Fang T, Lin H, Ma Y. Three-level anterior cervical discectomy and fusion with self-locking stand-alone polyetheretherketone cages. J Clin Neurosci. 2011 Nov;18(11):1505-9. Also available: http://dx.doi.org/10.1016/j.jocn.2011.02.045. PMID: 21924914.

43. Zhou J, Xia Q, Dong J, Li X, Zhou X, Fang T, Lin H. Comparison of stand-alone polyetheretherketone cages and iliac crest autografts for the treatment of cervical degenerative disc diseases. Acta Neurochir (Wien). 2011 Jan;153(1):115-22. PMID: 20924769.

44. Li Z, Wu W, Chen R, Huang Y, Chen X, Lin J. Could allograft bones combined with poly-ether-ether-ketone cages or titanium mesh cages be an alternative grafting method in the management of cervical spinal tuberculosis? World Neurosurg. 2019 Aug;128:e653-e659. Also available: http://dx.doi.org/10.1016/j.wneu.2019.04.226. PMID: 31054342.

45. Phan K, Pelletier MH, Rao PJ, Choy WJ, Walsh WR, Mobbs RJ. Integral fixation titanium/polyetheretherketone cages for cervical arthrodesis: evolution of cage design and early radiological outcomes and fusion rates. Orthop Surg. 2019 Feb;11(1):52-9. Also available: http://dx.doi.org/10.1111/os.12413. PMID: 30614216.

46. Zapolska G, Kwiatkowski M, Turek G, Mariak Z, Hermanowicz A. Biomechanical evaluation of single- and multi-level anterior cervical discectomy and fusion with polyetheretherketone cages: radiological and clinical outcomes. Neurol Neurochir Pol. 2019;53(5):358-62. Also available: http://dx.doi.org/10.5603/PJNNS.a2019.0040. PMID: 31538657.

47. Kim SH, Lee JK, Jang JW, Park HW, Hur H. Polyetheretherketone cage with demineralized bone matrix can replace iliac crest autografts for anterior cervical discectomy and fusion in subaxial cervical spine injuries. J Korean Neurosurg Soc. 2017 Mar;60(2):211-9. Also available: http://dx.doi.org/10.3340/jkns.2015.0203.014.

48. Luo J, Huang S, Gong M, Li L, Yu T, Zou X. Two-level anterior cervical discectomy and fusion using self-locking stand-alone polyetheretherketone cages with two anchoring clips placed in the upper and lower vertebrae, respectively. Eur J Orthop Surg Traumatol. 2015 Jul;25(Suppl 1):147-53. Epub 2015 Mar 4. Also available: http://dx.doi.org/10.1007/s00590-015-1613-6. PMID: 25733346.

49. Junaid M, Kalsoom A, Khalid M, Bukhari SS. Cervical disc replacement with polyetheretherketone cages: clinical experience with 151 cases. J Ayub Med Coll Abbottabad. 2014 Oct-Dec;26(4):444-7. PMID: 25672161.

50. Spallone A, Marchione P, Li Voti P, Ferrante L, Visocchi M. Anterior cervical discectomy and fusion with "mini-invasive" harvesting of iliac crest graft versus polyetheretherketone (PEEK) cages: a retrospective outcome analysis. Int J Surg. 2014 Dec;12(12):1328-32. Also available: http://dx.doi.org/10.1016/j.ijsu.2014.11.003. PMID: 25448654.

51. Chang M-Y, Chen M-H, Chang C-J, Huang J-S. Preliminary clinical experience with polyetheretherketone cages filled with synthetic crystallic semihydrate form of calcium sulfate for anterior cervical discectomy and fusion. Formosan J Surg. 2013 Aug;46(4):109-15. Also available: https://doi.org/10.1016/j.fjs.2013.04.005.

52. Dufour T, Huppert J, Louis C, Beaurain J, Stecken J, Aubourg L, Vila T. Radiological analysis of 37 segments in cervical spine implanted with a peek stand-alone device, with at least one year follow-up. Br J Neurosurg. 2010 Dec;24(6):633-40.

53. Hasegawa T, Ushirozako H, Shigeto E, Ohba T, Oba H, Mukaiyama K, Shimizu S, Yamato Y, Ide K, Shibata Y, Ojima T, Takahashi J, Haro H, Matsuyama Y. The titanium-coated PEEK cage maintains better bone fusion with the endplate than the PEEK cage 6 months after PLIF surgery: a multicenter, prospective, randomized study. Spine (Phila Pa 1976). 2020 Aug;45(15):E892-E902. Also available: http://dx.doi.org/10.1097/BRS.0000000000003464. PMID: 32675599.

54. Manabe H, Sakai T, Morimoto M, Tezuka F, Yamashita K, Takata Y, Sairyo K. Radiological outcomes of posterior lumbar interbody fusion using a titanium-coated PEEK cage. J Med Invest. 2019;66(1):119-22. Also available: http://dx.doi.org/10.2152/jmi.66.119. PMID: 31064922.

55. Wu WJ, Li Y, Hou TY, Cheng P, Zhang ZH, Xu JZ, Luo F. Application of new allogeneic lumbar fusion cage (Biocage) in single-segment lumbar degenerative disease: a prospective controlled study with follow-up for ³2 years. World Neurosurg. 2019 Jun;126:e1309-e1314. Also available: http://dx.doi.org/10.1016/j.wneu.2019.03.084. PMID: 30898751.

56. Heinz von der Hoeh N, Villa T, Galbusera F, Voelker A, Spiegl UA, Jarvers JS, Heyde CE. Analysis of a unilateral bridging cage for lumbar interbody fusion: 2-year clinical results and fusion rate with a focus on subsidence. World Neurosurg. 2018 Aug;116:e308-e314. Also available: http://dx.doi.org/10.1016/j.wneu.2018.04.195. PMID: 29738859.

57. Hoppe S, Albers CE, Elfiky T, Deml MC, Milavec H, Bigdon SF, Benneker LM. First results of a new vacuum plasma sprayed (VPS) titanium-coated carbon/PEEK composite cage for lumbar interbody fusion. J Funct Biomater. 2018 Mar 14;9(1):23. Also available: http://dx.doi.org/10.3390/jfb9010023.

58. Norotte G, Barrios C. Clinical and radiological outcomes after stand-alone ALIF for single L5-S1 degenerative discopathy using a PEEK cage filled with hydroxyapatite nanoparticles without bone graft. Clin Neurol Neurosurg. 2018 May;168:24-9 . Also available: http://dx.doi.org/10.1016/j.clineuro.2018.01.037. PMID: 29505978.

59. Lee N, Kim KN, Yi S, Ha Y, Shin DA, Yoon DH, Kim KS. Comparison of outcomes of anterior, posterior, and transforaminal lumbar interbody fusion surgery at a single lumbar level with degenerative spinal dsease. World Neurosurg. 2017 May;101:216-26. Also available: http://dx.doi.org/10.1016/j.wneu.2017.01.114. PMID: 28189865.

60. Mi J, Li K, Zhao X, Zhao CQ, Li H, Zhao J. Vertebral body Hounsfield units are associated with cage subsidence after transforaminal lumbar interbody fusion with unilateral pedicle screw fixation. Clin Spine Surg. 2017 Oct;30(8):E1130-E1136. Also available: http://dx.doi.org/10.1097/BSD.0000000000000490. PMID: 27906743.

61. Oh KW, Lee JH, Lee JH, Lee DY, Shim HJ. The correlation between cage subsidence, bone mineral density, and clinical results in posterior lumbar interbody fusion. Clin Spine Surg. 2017 Jul;30(6):E683-E689. Also available: http://dx.doi.org/10.1097/BSD.0000000000000315. PMID: 28632554.

62. Wang G, Han D, Cao Z, Guan H, Xuan T. Outcomes of autograft alone versus PEEK+ autograft interbody fusion in the treatment of adult lumbar isthmic spondylolisthesis. Clin Neurol Neurosurg. 2017 Apr;155:1-6. Also available: http://dx.doi.org/10.1016/j.clineuro.2017.01.020. PMID: 28187368.

63. Wrangel CV, Karakoyun A, Buchholz KM, Süss O, Kombos T, Woitzik J, Vajkoczy P, Czabanka M. Fusion rates of intervertebral polyetheretherketone and titanium cages without bone grafting in posterior interbody lumbar fusion surgery for degenerative lumbar instability. J Neurol Surg Rep. 2017 Nov;78(6):556-60. Also available: http://dx.doi.org/10.1055/s-0037-1604284. PMID: 28800665.

64. Deng QX, Ou YS, Zhu Y, Zhao ZH, Liu B, Huang Q, Du X, Jiang DM. Clinical outcomes of two types of cages used in transforaminal lumbar interbody fusion for the treatment of degenerative lumbar diseases: n-HA/PA66 cages versus PEEK cages. J Mater Sci Mater Med. 2016 Jun;27(6):102. Also available: http://dx.doi.org/10.1007/s10856-016-5712-7. PMID: 27091044.

65. Kuang L, Chen Y, Li L, Lü G, Wang B. Applying the mini-open anterolateral lumbar interbody fusion with self-anchored stand-alone polyetheretherketone cage in lumbar revision surgery. Biomed Res Int. 2016;2016:1758352. Also available: http://dx.doi.org/10.1155/2016/1758352. PMID: 27885355.

66. Mobbs RJ, Phan K, Assem Y, Pelletier M, Walsh WR. Combination Ti/PEEK ALIF cage for anterior lumbar interbody fusion: early clinical and radiological results. J Clin Neurosci. 2016 Dec;34:94-9. Also available: http://dx.doi.org/10.1016/j.jocn.2016.05.028. PMID: 27469413.

67. Schimmel JJP, Poeschmann MS, Horsting PP, Schönfeld DH, Limbeek JV, Pavlov PW. PEEK cages in lumbar fusion mid-term clinical outcome and radiologic fusion. Clin Spine Surg. 2016 Jun;29(5):E252-8. Also available: http://dx.doi.org/10.1097/BSD.0b013e31826eaf74. PMID: 27196005.

68. Ni J, Zheng Y, Liu N, Wang X, Fang X, Phukan R, Wood KB. Radiological evaluation of anterior lumbar fusion using PEEK cages with adjacent vertebral autograft in spinal deformity long fusion surgeries. Eur Spine J. 2015 Apr;24(4):791-9. Epub 2015 Jan 25. Also available: http://dx.doi.org/10.1007/s00586-014-3745-5. PMID: 25618451.

69. Allain J, Delecrin J, Beaurain J, Poignard A, Vila T, Flouzat-Lachaniette CH. Stand-alone ALIF with integrated intracorporeal anchoring plates in the treatment of degenerative lumbar disc disease: a prospective study on 65 cases. Eur Spine J. 2014 Sep 27;23(10):2136-43. Also available: http://dx.doi.org/10.1007/s00586-014-3364-1. PMID: 24952630.

70. Flouzat-Lachaniette CH, Ghazanfari A, Bouthors C, Poignard A, Hernigou P, Allain J. Bone union rate with recombinant human bone morphogenic protein-2 versus autologous iliac bone in PEEK cages for anterior lumbar interbody fusion. Int Orthop. 2014 Sep;38(9):2001-7. Also available: http://dx.doi.org/10.1007/s00264-014-2301-6. PMID: 24627122.

71. Malham GM, Parker RM, Ellis NJ, Blecher CM, Chow FY, Claydon MH. Anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2: a prospective study of complications. J Neurosurg Spine. 2014 Dec;21(6):851-60. Also available: http://dx.doi.org/10.3171/2014.8.SPINE13524. PMID: 25279655.

72. Nemoto O, Asazuma T, Yato Y, Imabayashi H, Yasuoka H, Fujikawa A. Comparison of fusion rates following transforaminal lumbar interbody fusion using polyetheretherketone cages or titanium cages with transpedicular instrumentation. Eur Spine J. 2014 Sep 27;23(10):2150-5. Also available: http://dx.doi.org/10.1007/s00586-014-3466-9. PMID: 25015180.

73. Behrbalk E, Uri O, Parks RM, Musson R, Soh RCC, Boszczyk BM. Fusion and subsidence rate of stand alone anterior lumbar interbody fusion using PEEK cage with recombinant human bone morphogenetic protein-2. Eur Spine J. 2013 Dec;22(12):2869-75. Also available: http://dx.doi.org/10.1007/s00586-013-2948-5. PMID: 23955421.

74. Jiya TU, Smit T, Van Royen BJ, Mullender M. Posterior lumbar interbody fusion using non resorbable poly-ether-ether- ketone versus resorbable poly-L-lactide-co-D, L-lactide fusion devices. Clinical outcome at a minimum of 2-year follow-up. Eur Spine J. 2011 Apr;20(4):618-22. PMID: 20842388.

75. Lee JH, Lee JH, Park JW, Lee HS. Fusion rates of a morselized local bone graft in polyetheretherketone cages in posterior lumbar interbody fusion by quantitative analysis using consecutive three-dimensional computed tomography scans. Spine J. 2011 Jul;11(7):647-53. PMID: 21620776.

76. Sethi A, Craig J, Bartol S, Chen W, Jacobsen M, Coe C, Vaidya R. Radiographic and CT evaluation of recombinant human bone morphogenetic protein-2-assisted spinal interbody fusion. AJR Am J Roentgenol. 2011 Jul;197(1):W128-33.

77. Akbary K, Quillo-Olvera J, Lin GX, Jo HJ, Kim JS. Outcomes of minimally invasive oblique lumbar interbody fusion in patients with lumbar degenerative disease with rheumatoid arthritis. J Neurol Surg Rep. 2019;80(3):162-8. Also available: http://dx.doi.org/10.1055/s-0038-1676301. PMID: 30677786.

78. Novak I, Košak R, Travnik L, Gorenšek M, Bošnjak K, Vengust R, Zupanc O. Polyetheretherketone (PEEK) cages for anterior column reconstruction in pyogenic vertebral osteomyelitis. J Orthop Surg (Hong Kong). 2019 May-Aug;27(2):2309499019842490. Also available: http://dx.doi.org/10.1177/2309499019842490. PMID: 30987501.

79. Rickert M, Fleege C, Tarhan T, Schreiner S, Makowski MR, Rauschmann M, Arabmotlagh M. Transforaminal lumbar interbody fusion using polyetheretherketone oblique cages with and without a titanium coating. Bone Joint J. 2017 Oct;99-B(10):1366-72. Also available: http://dx.doi.org/10.1302/0301-620X.99B10.BJJ-2016-1292.R2. PMID: 28963159.

80. Sclafani JA, Bergen SR, Staples M, Liang K, Raiszadeh R. Arthrodesis rate and patient reported outcomes after anterior lumbar interbody fusion utilizing a plasma-sprayed titanium coated PEEK interbody implant: a retrospective, observational analysis. Int J Spine Surg. 2017 Jan 13;11(1):17-23. Also available: http://dx.doi.org/10.14444/4004. PMID: 28377862.

81. Sembrano JN, Horazdovsky RD, Sharma AK, Yson SC, Santos ERG, Polly DW. Do lordotic cages provide better segmental lordosis versus nonlordotic cages in lateral lumbar interbody fusion (LLIF)? Clin Spine Surg. 2017 May;30(4):E338-E343. Also available: http://dx.doi.org/10.1097/BSD.0000000000000114. PMID: 28437335.

82. Struwe C, Hermann PC, Bornemann R, Plöger M, Roessler PP, Strauss AC, Rommelspacher Y, Koch EMW, Pflugmacher R. A novel PLIF PEEK interbody cage with an impactionless insertion technology: a case series with a mid-term follow up of three years. Technol Health Care. 2017;25(5):949-57. Also available: http://dx.doi.org/10.3233/THC-160721. PMID: 28759978.

83. Yang E, Cao L, Zhang G, Lian X, Xu J. Transpseudarthrosis osteotomy with interbody fusion for kyphotic spinal pseudarthrosis in ankylosing spondylitis by a single posterior approach: a retrospective study and a brief relevant literature review. Biomed Res Int. 2017;2017:4079849. Also available: http://dx.doi.org/10.1155/2017/4079849. PMID: 28875150.

84. Lin B, Yu H, Chen Z, Huang Z, Zhang W. Comparison of the PEEK cage and an autologous cage made from the lumbar spinous process and laminae in posterior lumbar interbody fusion. BMC Musculoskelet Disord. 2016 Aug 30;17(1):374. Also available: http://dx.doi.org/10.1186/s12891-016-1237-y. PMID: 27577978.

85. Shiban E, Janssen I, da Cunha PR, Rainer J, Stoffel M, Lehmberg J, Ringel F, Meyer B. Safety and efficacy of polyetheretherketone (PEEK) cages in combination with posterior pedicel screw fixation in pyogenic spinal infection. Acta Neurochir (Wien). 2016 Oct;158(10):1851-7. Also available: http://dx.doi.org/10.1007/s00701-016-2924-z. PMID: 27510825.

86. Lee JH, Lee DO, Lee JH, Shim HJ. Effects of lordotic angle of a cage on sagittal alignment and clinical outcome in one level posterior lumbar interbody fusion with pedicle screw fixation. Biomed Res Int. 2015 Jan 22;2015:523728. Also available: http://dx.doi.org/10.1155/2015/523728. PMID: 25685795.

87. Malham GM, Parker RM, Goss B, Blecher CM. Clinical results and limitations of indirect decompression in spinal stenosis with laterally implanted interbody cages: results from a prospective cohort study. Eur Spine J. 2015 Apr;24(Suppl 3):339-45. Epub 2015 Feb 14. Also available: http://dx.doi.org/10.1007/s00586-015-3807-3. PMID: 25681117.

88. Liu L, Lu ST, Liu AH, Hou WB, Cao WR, Zhou C, Yin YX, Yuan KS, Liu HJ, Zhang MG, Zhang HJ. Comparison of complications in cranioplasty with various materials: a systematic review and meta-analysis. Br J Neurosurg. 2020 Apr;1-9. Also available: http://dx.doi.org/10.1080/02688697.2020.1742291. PMID: 32233810.

89. Asencio-Cortés C, Salgado-López L, Muñoz-Hernandez F, de Quintana-Schmidt C, Rodríguez-Rodríguez R, Álvarez-Holzapfel MJ, Conesa G. Long-term safety and performance of a polymeric clamplike cranial fixation system. World Neurosurg. 2019 Jun;126:e758-e764. Also available: http://dx.doi.org/10.1016/j.wneu.2019.02.146. PMID: 30853518.

90. Bianchi F, Signorelli F, Di Bonaventura R, Trevisi G, Pompucci A. One-stage frame-guided resection and reconstruction with PEEK custom-made prostheses for predominantly intraosseous meningiomas: technical notes and a case series. Neurosurg Rev. 2019 Sep;42(3):769-75. Also available: http://dx.doi.org/10.1007/s10143-019-01104-5. PMID: 31055698.

91. Morselli C, Zaed I, Tropeano MP, Cataletti G, Iaccarino C, Rossini Z, Servadei F. Comparison between the different types of heterologous materials used in cranioplasty: a systematic review of the literature. J Neurosurg Sci. 2019;63(6):723-36. Also available: http://dx.doi.org/10.23736/S0390-5616.19.04779-9. PMID: 31599560.

92. Oliver JD, Banuelos J, Abu-Ghname A, Vyas KS, Sharaf B. Alloplastic cranioplasty reconstruction: a systematic review comparing outcomes with titanium mesh, polymethyl methacrylate, polyether ether ketone, and norian implants in 3591 adult patients. Ann Plast Surg. 2019 May;82(5S Suppl 4):S289-S294. Also available: http://dx.doi.org/10.1097/SAP.0000000000001801. PMID: 30973834.

93. Nguyen PD, Khechoyan DY, Phillips JH, Forrest CR. Custom CAD/CAM implants for complex craniofacial reconstruction in children: our experience based on 136 cases. J Plast Reconstr Aesthet Surg. 2018 Nov;71(11):1609-17. Also available: http://dx.doi.org/10.1016/j.bjps.2018.07.016. PMID: 30220563.

94. van de Vijfeijken SECM, Münker TJAG, Spijker R, Karssemakers LHE, Vandertop WP, Becking AG, Ubbink DT, CranioSafe Group. Autologous bone is inferior to alloplastic cranioplasties: safety of autograft and allograft materials for cranioplasties, a systematic review. World Neurosurg. 2018 Sep;117:443-452.e8. Also available: http://dx.doi.org/10.1016/j.wneu.2018.05.193. PMID: 29879511.

95. Zhang Q, Yuan Y, Li X, Sun T, Zhou Y, Yu H, Guan J. A large multicenter retrospective research on embedded cranioplasty and covered cranioplasty. World Neurosurg. 2018 Apr;112:e645-e651. Also available: http://dx.doi.org/10.1016/j.wneu.2018.01.114. PMID: 29374612.

96. Brandicourt P, Delanoé F, Roux FE, Jalbert F, Brauge D, Lauwers F. Reconstruction of cranial vault defect with polyetheretherketone implants. World Neurosurg. 2017 Sep;105:783-9. Also available: http://dx.doi.org/10.1016/j.wneu.2017.04.049. PMID: 28434964.

97. Mrad MA, Murrad K, Antonyshyn O. Analyzing the cost of autogenous cranioplasty versus custom-made patient-specific alloplastic cranioplasty. J Craniofac Surg. 2017 Jul;28(5):1260-3. Also available: http://dx.doi.org/10.1097/SCS.0000000000003708. PMID: 28582300.

98. Punchak M, Chung LK, Lagman C, Bui TT, Lazareff J, Rezzadeh K, Jarrahy R, Yang I. Outcomes following polyetheretherketone (PEEK) cranioplasty: systematic review and meta-analysis. J Clin Neurosci. 2017 Jul;41:30-5. Also available: http://dx.doi.org/10.1016/j.jocn.2017.03.028. PMID: 28377284.

99. Jonkergouw J, van de Vijfeijken SECM, Nout E, Theys T, Van de Casteele E, Folkersma H, Depauw PRAM, Becking AG. Outcome in patient-specific PEEK cranioplasty: a two-center cohort study of 40 implants. J Craniomaxillofac Surg. 2016;44(9):1266-72. Also available: http://dx.doi.org/10.1016/j.jcms.2016.07.005. PMID: 27524384.

100. Liang ES, Tipper G, Hunt L, Gan PYC. Cranioplasty outcomes and associated complications: a single-centre observational study. Br J Neurosurg. 2016 Jan 2;30(1):122-7. Also available: http://dx.doi.org/10.3109/02688697.2015.1080216. PMID: 26328774.

101. Mundinger GS, Latham K, Friedrich J, Louie O, Said H, Birgfeld C, Ellenbogen R, Hopper RA. Management of the repeatedly failed cranioplasty following large postdecompressive craniectomy: establishing the efficacy of staged free latissimus dorsi transfer/tissue expansion/custom polyetheretherketone implant reconstruction. J Craniofac Surg. 2016 Nov;27(8):1971-7. Also available: http://dx.doi.org/10.1097/SCS.0000000000003043. PMID: 28005736.

102. Alonso-Rodriguez E, Cebrián JL, Nieto MJ, Del Castillo JL, Hernández-Godoy J, Burgueño M. Polyetheretherketone custom-made implants for craniofacial defects: report of 14 cases and review of the literature. J Craniomaxillofac Surg. 2015 Sep;43(7):1232-8. Also available: http://dx.doi.org/10.1016/j.jcms.2015.04.028. PMID: 26032759.

103. O'Reilly EB, Barnett S, Madden C, Welch B, Mickey B, Rozen S. Computed-tomography modeled polyether ether ketone (PEEK) implants in revision cranioplasty. J Plast Reconstr Aesthet Surg. 2015 Mar;68(3):329-38. Also available: http://dx.doi.org/10.1016/j.bjps.2014.11.001. PMID: 25541423.

104. Thien A, King NKK, Ang BT, Wang E, Ng I. Comparison of polyetheretherketone and titanium cranioplasty after decompressive craniectomy. World Neurosurg. 2015 Feb;83(2):176-80. Also available: http://dx.doi.org/10.1016/j.wneu.2014.06.003. PMID: 24909393.

105. Rosenthal G, Ng I, Moscovici S, Lee KK, Lay T, Martin C, Manley GT. Polyetheretherketone implants for the repair of large cranial defects: a 3-center experience. Neurosurgery. 2014;75(5):523-8. Also available: http://dx.doi.org/10.1227/NEU.0000000000000477. PMID: 24979096.

106. Cofano F, Di Perna G, Monticelli M, Marengo N, Ajello M, Mammi M, Vercelli G, Petrone S, Tartara F, Zenga F, Lanotte M, Garbossa D. Carbon fiber reinforced vs titanium implants for fixation in spinal metastases: a comparative clinical study about safety and effectiveness of the new "carbon-strategy". J Clin Neurosci. 2020 May;75:106-11. Also available: http://dx.doi.org/10.1016/j.jocn.2020.03.013. PMID: 32173153.

107. Tarallo L, Giorgini A, Novi M, Zambianchi F, Porcellini G, Catani F. Volar PEEK plate for distal radius fracture: analysis of adverse events. Eur J Orthop Surg Traumatol. 2020 Oct;30(7):1293-8. Epub 2020 May 20. Also available: http://dx.doi.org/10.1007/s00590-020-02701-7. PMID: 32435847.

108. Allemann F, Halvachizadeh S, Rauer T, Pape HC. Clinical outcomes after carbon-plate osteosynthesis in patients with distal radius fractures. Patient Saf Surg. 2019 Sep 4;13:30. Also available: http://dx.doi.org/10.1186/s13037-019-0210-8. PMID: 31516553.

109. Järvinen S, Suojanen J, Kormi E, Wilkman T, Kiukkonen A, Leikola J, Stoor P. The use of patient specific polyetheretherketone implants for reconstruction of maxillofacial deformities. J Craniomaxillofac Surg. 2019 Jul;47(7):1072-6. Also available: http://dx.doi.org/10.1016/j.jcms.2019.03.018. PMID: 31103433.

110. Padolino A, Porcellini G, Guollo B, Fabbri E, Kiran Kumar GN, Paladini P, Merolla G. Comparison of CFR-PEEK and conventional titanium locking plates for proximal humeral fractures: a retrospective controlled study of patient outcomes. Musculoskelet Surg. 2018 Oct;102(Suppl 1):49-56. Also available: http://dx.doi.org/10.1007/s12306-018-0562-8. PMID: 30343471.

111. Roberson TA, Momaya AM, Adams K, Long CD, Tokish JM, Wyland DJ. High tibial osteotomy performed with all-PEEK implants demonstrates similar outcomes but less hardware removal at minimum 2-year follow-up compared with metal plates. Orthop J Sports Med. 2018 Mar 12;6(3):2325967117749584. Also available: http://dx.doi.org/10.1177/2325967117749584. PMID: 29560369.

112. Di Maggio B, Sessa P, Mantelli P, Maniscalco P, Rivera F, Calori GM, Bisogno L, Scaravilli G, Caforio M. PEEK radiolucent plate for distal radius fractures: multicentre clinical results at 12 months follow up. Injury. 2017 Oct;48(Suppl 3):S34-S38. Also available: http://dx.doi.org/10.1016/S0020-1383(17)30655-1. PMID: 29025607.

113. Guzzini M, Lanzetti RM, Lupariello D, Morelli F, Princi G, Perugia D, Ferretti A. Comparison between carbon-peek plate and conventional stainless steal plate in ankle fractures. A prospective study of two years follow up. Injury. 2017 Jun;48(6):1249-52. Also available: http://dx.doi.org/10.1016/j.injury.2017.03.035. PMID: 28366469.

114. Katthagen JC, Ellwein A, Lutz O, Voigt C, Lill H. Outcomes of proximal humeral fracture fixation with locked CFR-PEEK plating. Eur J Orthop Surg Traumatol. 2017 Apr;27(3):351-8. Also available: http://dx.doi.org/10.1007/s00590-016-1891-7. PMID: 27915444.

115. Cotic M, Vogt S, Feucht MJ, Saier T, Minzlaff P, Hinterwimmer S, Imhoff AB. Prospective evaluation of a new plate fixator for valgus-producing medial open-wedge high tibial osteotomy. Knee Surg Sports Traumatol Arthrosc. 2015 Dec;23(12):3707-16. Also available: http://dx.doi.org/10.1007/s00167-014-3287-8. PMID: 25209206.

116. Schliemann B, Hartensuer R, Koch T, Theisen C, Raschke MJ, Kösters C, Weimann A. Treatment of proximal humerus fractures with a CFR-PEEK plate: 2-year results of a prospective study and comparison to fixation with a conventional locking plate. J Shoulder Elbow Surg. 2015 Aug;24(8):1282-8. Also available: http://dx.doi.org/10.1016/j.jse.2014.12.028. PMID: 25704209.

117. Cotic M, Vogt S, Hinterwimmer S, Feucht MJ, Slotta-Huspenina J, Schuster T, Imhoff AB. A matched-pair comparison of two different locking plates for valgus-producing medial open-wedge high tibial osteotomy: peek-carbon composite plate versus titanium plate. Knee Surg Sports Traumatol Arthrosc. 2015 Jul;23(7):2032-40. Also available: http://dx.doi.org/10.1007/s00167-014-2914-8. PMID: 24562634.

118. Tarallo L, Mugnai R, Adani R, Zambianchi F, Catani F. A new volar plate made of carbon-fiber-reinforced polyetheretherketon for distal radius fracture: analysis of 40 cases. J Orthop Traumatol. 2014 Nov 26;15(4):277-83. Also available: http://dx.doi.org/10.1007/s10195-014-0311-1. PMID: 25017027.

119. Velonakis G, Filippiadis D, Spiliopoulos S, Brountzos E, Kelekis N, Kelekis A. Evaluation of pain reduction and height restoration post vertebral augmentation using a polyether ether ketone (PEEK) polymer implant for the treatment of split (Magerl A2) vertebral fractures: a prospective, long-term, non-randomized study. Eur Radiol. 2019 Aug;29(8):4050-7. Also available: http://dx.doi.org/10.1007/s00330-018-5867-3. PMID: 30511178.

120. Korovessis P, Mpountogianni E, Syrimpeis V, Baikousis A, Tsekouras V. Percutaneous injection of strontium containing hydroxyapatite versus polymethacrylate plus short-segment pedicle screw fixation for traumatic A2- and A3/AO-type fractures in adults. Adv Orthop. 2018 Mar 5;2018:6365472. Also available: http://dx.doi.org/10.1155/2018/6365472. PMID: 29692935.

121. Beall DP, Coe JD, McIlduff M, Bloch D, Hornberger J, Warner C, Tutton SM. Serious adverse events associated with readmission through one year after vertebral augmentation with either a polyetheretherketone implant or balloon kyphoplasty: Follow-up analysis of the KAST randomized controlled trial comparing the kiva vertebral compression fracture treatment system. Pain Physician. 2017 Sep;20(6):521-8. PMID: 28934783.

122. Korovessis P, Vardakastanis K, Repantis T, Vitsas V. Transpedicular vertebral body augmentation reinforced with pedicle screw fixation in fresh traumatic A2 and A3 lumbar fractures: comparison between two devices and two bone cements. Eur J Orthop Surg Traumatol. 2014 Jul;24 Suppl 1:S183-91. Also available: http://dx.doi.org/10.1007/s00590-013-1296-9. PMID: 23982115.

123. Raslan F, Koehler S, Berg F, Rueckriegel S, Ernestus RI, Meinhardt M, Westermaier T. Vertebral body replacement with PEEK-cages after anterior corpectomy in multilevel cervical spinal stenosis: a clinical and radiological evaluation. Arch Orthop Trauma Surg. 2014 May;134(5):611-8. Also available: http://dx.doi.org/10.1007/s00402-014-1972-1. PMID: 24676649.

124. Heary RF, Kheterpal A, Mammis A, Kumar S. Stackable carbon fiber cages for thoracolumbar interbody fusion after corpectomy: long-term outcome analysis. Neurosurgery. 2011 Mar;68(3):810-8. Also available: http://dx.doi.org/10.1227/NEU.0b013e3182077a9f. PMID: 21311306.

125. Koban O, Ögrenci A, Akar EA, Uyanik AS, Yilmaz M, Dalbayrak S. Radiological and clinical comparisons of the patients with rheumatoid arthritis operated with rigid and dynamic instrumentation systems due to lumbar degenerative spinal diseases. J Orthop Sci. 2020 Jun 26;S0949-2658(20):30150-0. Also available: http://dx.doi.org/10.1016/j.jos.2020.05.011. PMID: 32600905.

Appendix F. Surveillance Event Reports – PSO and Accident Investigation

Provided with this report as separate Excel spreadsheet.

Appendix G. Regulatory and Manufacturer Safety Alerts

Specific search terms are provided here. The associated alerts are provided with this report as a separate PDF.