European Cells and Materials Vol. 40 2020 (pages 1-20) DOI: 10.22203/eCM.v040a01 ISSN 1473-2262

THE CURRENT STATE OF PEEK IMPLANT OSSEOINTEGRATION AND FUTURE PERSPECTIVES: A SYSTEMATIC REVIEW

N.M. AlOtaibi[1,2], K.B. Naudi[3], D.I. Conway[4] and A.F. Ayoub[1,*]

[1] University of Glasgow, Glasgow University Dental Hospital and School/Oral and Maxillofacial Surgery, Glasgow, UK
[2] King Saud University, Oral and Maxillofacial Surgery/Dental College, Riyadh, Saudi Arabia
[3] University of Glasgow, Glasgow University Dental Hospital and School/Oral Surgery, Glasgow, UK
[4] University of Glasgow, Glasgow University Dental Hospital and School/Public Health, Glasgow, UK

Abstract

Polyetheretherketone (PEEK) has been considered as an alternative to replace surgical metal implants. Several medical applications, including dental and orthopaedic implants, need confirmed osseointegration before functional loading. The present study aims at providing a comprehensive systematic review of the evidence on PEEK implants' osseointegration. A systematic search was conducted using Cochrane library, MEDLINE (PubMed), Ovid MEDLINE, Web of Science and EMBASE databases. Publications were identified in accordance with specific inclusion and exclusion criteria. Eligibility screening, data extraction and quality assessment were performed. The review protocol was registered in PROSPERO (CRD42018116061). A total of 55 articles were reviewed and 29 of the most relevant that met the inclusion criteria were selected. Heterogeneity was identified among the included studies.

Several approaches have been applied to enhance PEEK osseointegration, with most *in vivo* studies conducted on small-scale animal models but no study evaluating the osseointegration of PEEK under cyclic loading. However, PEEK modifications are demonstrated to enhance osseointegration preclinically. Collectively, the present review shows a shortage of evidence, including a lack of comprehensive assessment of osseointegration, the need for large-animal-model tests, the need to assess the effect of loading on the implants and the lack of randomised controlled clinical trials.

Keywords: Polyetheretherketone, dental implant, coated polyetheretherketone, biomaterials, synthetic polymers, osseointegration, polyetheretherketone composite.

***Address for correspondence**: Prof Ashraf F. Ayoub PhD, FDS RCS (Edin), FDS RCPS (Glas), MDS Professor of Oral and Maxillofacial Surgery, Honorary Consultant in Oral and Maxillofacial Surgery, University of Glasgow, Glasgow, UK.
Telephone number: +44 1412119649 Fax number: +44 1412119601 Email: ashraf.ayoub@glasgow.ac.uk

Introduction

Currently available dental implants for clinical use are made of titanium, its alloys and zirconium. Titanium has excellent biocompatibility and osseointegration properties. Therefore, it is widely used as a dental implant (Sidambe, 2014). Titanium dental implants have excellent success rates (Reinhardt and Beikler, 2014), however, they are associated with bone resorption over time around the crest of the alveolar ridge due to the mismatch between the elastic modulus of the titanium implant and that of the alveolar bone (Gao *et al.*, 2019; Schwitalla and Müller, 2013; Shibata *et al.*, 2015; Zivic *et al.*, 2017). The main disadvantage of titanium is its high elasticity modulus when compared to that of bone, which leads to the concentration of loading pressure on to the implant, resulting in stress shielding with reduced loading on the surrounding bone. This leads to bone resorption, according to Wolff's law (Kini and Nandeesh, 2012). In addition, radiographic imaging of the jaw bones for the assessment of pathological conditions can be affected due to the scattered radiation around the dental implants, resulting in a potential reduction in the quality of radiographs, impacting upon the diagnosis. Special precautions are required for

magnetic resonance imaging (MRI) of jaw bones that have metallic dental implants (Gupta *et al.*, 2015). Furthermore, while sensitivity to titanium is rare, it has been reported in up to 0.6 % of cases (Sicilia *et al.*, 2008). All the above challenges have driven the development of alternative implant materials.

Polyetheretherketone (PEEK) is a member of the high-performance semi-crystalline thermoplastic polymers, first produced by English scientists in 1978 (Cinderey and Rose, 1979; Eschbach, 2000) (Fig. 1). In the late 1990s, PEEK was introduced as a candidate for replacing metal implants in several medical fields, including orthopaedics, craniofacial and spine surgery. To date, several orthopaedic and spinal implants fabricated from PEEK have been approved by the Food and Drug Administration (FDA) (Kurtz, 2012). It is biocompatible, physically and chemically stable and biologically inert (Elawadly *et al.*, 2017; Khoury *et al.*, 2015; Ma and Tang, 2014). Moreover, it has low plaque accumulation and bacterial colonisation (Najeeb *et al.*, 2016; Skirbutis *et al.*, 2017; Volpe *et al.*, 2008). PEEK has excellent mechanical properties that support its potential application as an implant, but its inertness prevents osseointegration. Overcoming this limitation remains the greatest challenge for PEEK implant clinical applications.

Osseointegration of dental implants is an essential factor for the clinical application of alloplastic materials. Clinically, osseointegration is defined as asymptomatic rigid fixation of alloplastic materials in the bone under functional loading (Zarb and Albrektsson, 1991). The microscopic definition of osseointegration is the direct contact between the implant surface and the surrounding bone without interposition of any fibrous or connective tissue (Albrektsson *et al.*, 2017). Recent studies referred to osseointegration as the body's reaction (bone) to isolate the foreign body (implant) (Albrektsson *et al.*, 2017). Therefore, understanding osseointegration at all levels (clinical, histological and conceptional) is crucial.

The present review assessed, for the first time, the world-wide literature on PEEK implants to address the poor osseointegration of PEEK implants for dental and orthopaedic applications. The objective was to assess the strength of the available evidence, with a narrative synthesis of the findings on the current state of osseointegration of PEEK implants and future perspectives. An in-depth critique of the bioactive properties, cell/bone integration, success criteria and limitations is discussed.

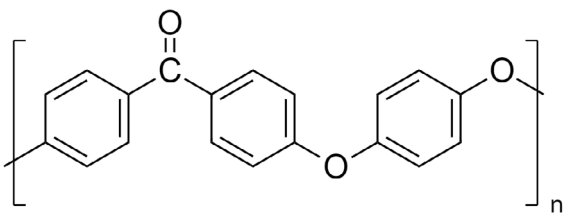


Fig. 1. PEEK chemical formula.

Materials and Methods

Protocol and registration

The complete protocol method was registered in advance. The review was registered in an international prospective register of systematic reviews, PROSPERO (Chien *et al.*, 2012). The PROSPERO registration number is CRD42018116061 (Web ref. 1). The review is reported in accordance with the checklist of the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR 2) instrument and Risk of Bias in Systematic Reviews (ROBIS) tool (Shea *et al.*, 2017; Web ref. 2).

Focus questions

The following focus questions were developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, which were constructed according to population, intervention, comparison and outcome (PICO) principles (Moher *et al.*, 2009).

- Would modified PEEK implants osseointegrate in heathy candidates?
- What is the most recommended method to improve PEEK osseointegration?

Population

All studies that aimed at evaluating PEEK implant osseointegration were included with no restriction on study design. These studies could involve healthy humans and animals with no systemic disease.

Literature search strategy

According to the PRISMA guidelines, a comprehensive search was conducted electronically and manually through Cochrane Library, MEDLINE (PubMed), Ovid MEDLINE, Web of Science and EMBASE databases to locate articles focusing on the osseointegration of PEEK implants and methods of modification. Various combinations of keywords were used in the search process, including "polyetheretherketone", "PEEK", "PEEK composite", "implant", "osseointegration", "surface coated PEEK", "bioactive PEEK", "dental implant", "orthopaedic implant", "ketones" and "polymer". Only publications in English were included, with no restrictions on the year of publication. Manual search for literature not discovered in the above sources was conducted using Google and Google Scholar search engines. Furthermore, the reference lists of all included relevant articles and reviews, along with articles identified during the screening process, were examined to identify other potentially eligible studies. The full-text articles were assessed according to the following inclusion criteria:

- *in vitro/in vivo* studies evaluating the different types of PEEK modifications, coatings and osseointegration potential;
- *in vivo* studies carried out using healthy animals;
- studies involving diagnostic parameters and/or clinical, histological, histomorphometric, mechanical and/or radiographic tests;
- minimum follow-up of 3 weeks post operation.

Exclusion criteria were:

- *in vitro* studies only;
- non-English language;
- full text not available;
- systematic reviews.

Screening strategy

Following the initial systematic search, titles and abstracts of all potentially related references were screened and evaluated to assess the suitability for full-text inclusion. Then, retrieved studies were independently assessed for eligibility according to the pre-specified inclusion and exclusion criteria, not considering their results.

Data extraction

Data were independently collected from the included studies in form of parameters, according to the aims and objectives of the review. Data were extracted by one reviewer and checked for accuracy by the second and third reviewers. The second reviewer selected random samples of the included studies and performed the data extraction independently to assess their sensitivity and specificity. The extracted data variables are listed below.

Data items

Data were extracted and organised in the following fields (Table 1).

- Study: author and year of publication;
- model: animal model used;
- duration: period of implant healing;
- type of modification: method used to modify PEEK;
- finding/outcome: bone formation and osseointegration;
- BIC: bone implant contact in histological assessment;
- evaluation method: methods used to assess osseointegration of PEEK implant;
- mechanical test: type of mechanical testing, if performed;
- comparator: control implant;
- implant design: a schematic drawing to illustrate the shape and the design of the implant (illustrations not to scale).

Assessment of methodology

Assessment of the methodological validity of the included studies was performed using the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE)'s risk of bias (RoB) tool criteria (SYRCLE's RoB tool) based on the Cochrane collaboration bias summary for potential bias (Hooijmans *et al.*, 2014) and including 10 key domains. Heterogeneity among the included studies was evaluated to determine the possibility of a meta-analysis.

Results

Study selection

The initial search identified 140 results (Fig. 2). 137 articles were found by electronic searches and 3 additional articles through manual searches of reference lists. 36 duplicated papers were removed. A preliminary exclusion was performed on 49 articles based on reviewing titles and abstracts. The inclusion and exclusion criteria were applied to 55 articles. Finally, 29 studies were included in the systematic review.The language restriction was applied according to the registered PROSPERO protocol. However, during the manual search of the "grey" literature, no study published in non-English language was found.

Quality assessment

The results of RoB evaluation for each included study are summarised in Table 2. Only 1 study was classified as at a low risk of bias (Guillot *et al.*, 2016). 5 studies appeared to have a high risk of bias (Hassan *et al.*, 2018; Nakahara *et al.*, 2012; Ouyang *et al.*, 2016; Poulsson *et al.*, 2013; Wang *et al.*, 2014), while the remaining 24 studies were considered as having an unclear risk of bias.

Statistical analysis

A meta-analysis could not be conducted due to the heterogeneity of the included studies. A narrative synthesis was performed based on recency of publication and study quality.

Table 1. Characteristics of the included studies. BV/TV: percentage bone volume; BIC: bone to implant contact; BA: bone area; BAR: bone apposition rate; TbTh: trabecular thickness; TbN: trabecular number; CRF: carbon-fibre-reinforced; PEEK: polyetheretherketone; HA: hydroxyapatite; Ti: titanium; SN: silicon nitride; SLA: sandblasted, large grit and acid-etched (Straumann implant); MAR: mineral apposition rate; YSZ: yttria-stabilised zirconia; BMD: bone mineral density; BV: bone volume; AD + MW: microwave processing; AD + MW + AC: microwave plus autoclave processing; PPP: poly(para-phenylene); TiO_2: titanium dioxide; ANAB: accelerated neutral atom beam; SEM: scanning electron microscopy; µCT: micro-computed tomography.

Study	Model/duration	Type of modification	Finding/outcome	BIC	Evaluation method	Mechanical test	Implant design/ comparator
Koch *et al.*, 2009	Dog split mouth model 4 months	A comparative study between different implants including uncoated zirconia, calcium-liberating TiO_2-coated zirconia, Ti implant and PEEK	All implants were osseointegrated clinically and histologically	PEEK: 26.8 % Ti: 41.2 % Uncoated zirconia: 59.2 % Coated zirconia: 58.3 % Connective tissue was found around PEEK implant	Histomorphometry	N/A	Screw/thread  Ti
Nakahara *et al.*, 2012	Rabbit femur 6 and 12 weeks	HA coating for CRF-PEEK and Ti	Direct bone formation on coated implants that increased in time	Two implants/condition included for histological evaluation. The percentage of BIC at 6 and 12 weeks was larger in coated implants when compared to uncoated ones	Histology Pull-out	At 6 weeks uncoated CRF-PEEK: 7.7 MPa Uncoated Ti: 7.8 MPa HA/CRF-PEEK: 15.7 MPa HA/Ti: 14.1 MPa At 12 weeks uncoated CRF-PEEK: 8.3 MPa Uncoated Ti: 15 MPa HA/CRF-PEEK: 17.4 MPa HA/Ti: 14.2 MPa	Smooth  uncoated CRF-PEEK and Ti
Barkarmo *et al.*, 2012	Rabbit femur 6 weeks	n-HA spin coating	7 implants failed; 3 of them were coated implants	BIC and BA were larger in the coated implants than in the uncoated ones, without statistically significant difference. BIC of coated and uncoated implant was 16 ± 4.7 % and 13 ± 9.3 %, respectively. BA was 52 ± 9.5 % and 45 ± 11.9 %, respectively	Histology Histomorphometry	N/A	Smooth  uncoated PEEK
Webster *et al.*, 2012	Rat calvaria bacteria-induced model (*Staphylococcus epidemididis*) 3, 7, 14 and 90 d	No-modification comprehensive study to evaluate the anti-infective and osseointegration properties of SN, PEEK and Ti	Both PEEK and Ti showed no stability at 3 and 7 d in the control group. The new bone formation in the absence of bacterial injection was: PEEK: 24 % Ti: 36 % SN: 69 % Live bacteria around PEEK were 88 %, around Ti 21 % and none adjacent to SN	BIC values at 90 d without bacterial injection PEEK: 8 % Ti: 19 % SN: 59 % with bacterial injection PEEK: 5 % Ti: 9 % SN: 23 %	Histomorphometry Push out	For both conditions (with and without bacterial injection) SN implants showed significantly more push-out strength when compared to PEEK and Ti	Smooth  no bacterial injection

Study	Model/duration	Type of modification	Finding/outcome	BIC	Evaluation method	Mechanical test	Implant design/ comparator
Poulsson *et al.*, 2014	Sheep tibia and femur 4, 12 and 26 weeks	Oxygen plasma treatment on moulded and machined PEEK OPTIMA (well known medical grade PEEK)	Microroughness by machined process had significantly enhanced BIC and push-out values at all time points	Plasma treatment improved early phase osseointegration. Also, it was related to less fibrous tissue directly on the implant surface. Bone biomarkers' values were higher for all the implants at 4 weeks postoperatively and decreased at 12 weeks. BIC values were higher, despite not statistically significant, for the plasma-treated implant when compared to an untreated implant	Histology Bone labelling Push-out	Cancellous bone implants showed increased values with time for all groups. For the cortical bone implants, no statistically significant differences were observed over time, except for the values of moulded PEEK at 12 and 26 weeks, which were significantly higher at 26 weeks	Smooth  moulded and machined PEEK OPTIMA without plasma treatment
Xu *et al.*, 2014	Beagle dog; immediate implant after mandibular premolar extraction 4 weeks	n-HA biocomposite (PEEK/n-HA/CRF) HA: 25 wt % CRF: 15 wt % PEEK: 60 wt % followed by TiO_2 blasting with oxygen plasma treatment (p-m-PEEK/n-HA/CRF) or only oxygen plasma treatment (p-PEEK/n-HA/CRF)	p-m-PEEK/n-HA/CRF showed a significantly more BV/TV and TbTh than the other groups	Distinct osseointegration of p-PEEK/n-HA/CRF implant while more new bone formed around p-m-PEEK/n-HA/CRF implant. Newly formed bone biomarkers continuously deposited on the three biocomposite surfaces with dominant tetracycline uptake on p-m-PEEK/n-HA/CRF	µCT Histology Bone labelling Push-out	The average maximum push-out from Ti, PEEK/n-HA/CRF, p-PEEK/n-HA/CF and p-m-PEEK/n-HA/CRF were 21.7, 18.7, 39.2 and 51.3 N, respectively	Screw/thread  Ti grade 2
Johansson *et al.*, 2014	Rabbit tibia 3 and 12 weeks	n-HA coating	N/A	N/A	Removal torque test	HA-coated PEEK showed significantly higher removal torque values after both healing periods At 3 weeks PEEK: 7.18 Ncm HA/PEEK: 13 Ncm At 12 weeks PEEK: 5.58 Ncm HA/PEEK: 9.75 Ncm	Screw/thread  uncoated PEEK
Barkarmo *et al.*, 2014	Rabbit tibia and femur 6 weeks	n-HA coating	Coated implant revealed more bone formation when compared to uncoated one	Both BIC and BA for the coated implant demonstrated significantly higher mean values when compared to uncoated implant. Mean BIC values were 39 ± 14 % and 33 ± 12 % respectively, while the BA of the best three consecutive threads were 90 ± 3 % and 87 ± 4 %, respectively	Histomorphometry (femur) Removal torque test (tibia)	HA-coated PEEK showed significantly higher removal torque values when compared to uncoated PEEK (15.4 ± 8.8 Ncm and 8.5 ± 5.7 Ncm, respectively)	Screw/thread  uncoated PEEK

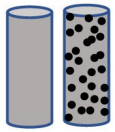
Study	Model/duration	Type of modification	Finding/outcome	BIC	Evaluation method	Mechanical test	Implant design/ comparator
Wang *et al.*, 2014	Beagle dog, immediate implant after 3rd and 4th mandibular premolar extraction (*in vitro Staphylococcus* mutans) 4 and 8 weeks	n-FHA/PEEK composite n-FHA: 40 wt % PEEK: 60 wt %	Significantly higher BV/TV, TbTh and TbN values for the biocomposite when compared to pure PEEK at both time points. n-FHA/PEEK demonstrated good antibacterial activity *in vitro*	n-FHA/PEEK showed significantly more BIC than PEEK. This finding was consistent with the bone biomarkers, with more bone regeneration and remodelling around the n-FHA/PEEK when compared to PEEK	µCT Histology Histomorphometry Bone labelling	N/A	Screw/thread  unmodified PEEK
Lu *et al.*, 2015	Rat femur 8 weeks	Tantalum nanoparticles implantation by plasma immersion ion implantation (PIII) for 30 min (Ta-30) and 120 min (Ta-120)	Bone volume of Ta-PIII groups was larger than PEEK. Ta-30 showed the largest bone volume among the three groups. Also, the percentage of bone labelling of TA-30 was significantly larger than in the remaining groups	More new bone formed after Ta-PIII modification, especially the Ta-30. A fibrous tissue was formed around unmodified PEEK. BIC of Ta-30 was 54.89 ± 3.13 %, which was a significantly higher value than both Ta-120 (39.94 ± 2.41 %) and PEEK (19.60 ± 6.17 %)	µCT Histology Bone labelling	N/A	Smooth  uncoated PEEK
Khoury *et al.*, 2015	Sheep hind limb, bilaterally 4 and 12 weeks	PEEK surface modified by ANAB	An excellent bone formation on the ANAB implant was observed when compared to the lack of bone ingrowth on the control. Thick fibrous tissue surrounded the uncoated implant	Direct bone contact with ANAB/PEEK at 4 weeks. BIC at 12 weeks significantly increased 3.9-fold when compared to unmodified PEEK in cancellous epiphyseal bone (58.16 ± 23.67 and 18.8 ± 13.5 %, respectively). Mid-diaphyseal cortical implants showed improved BIC of tested implants, with no statistically significant differences when compared to control	µCT Histomorphometry Push-out	At 4 weeks: significant increase of bone bonding strength of ANAB/PEEK when compared to PEEK (1282.4 ± 252.7 N/mm² and 600 ± 313 N/mm², 43255.3 ± 1527.3 KPa and 2219.6 ± 1954.1 KPa, respectively). At 12 weeks: bone bonding stiffness was significantly increased by 2.17-fold for ANAB/PEEK. The interface strength was significantly higher for ANAB/PEEK than for control (4068 ± 1197 KPa and 1959 ± 1445 KPa, respectively)	Smooth  unmodified PEEK
Lee *et al.*, 2015	Minipig iliac and intervertebral cage (spine model) 8 weeks	Cold spray of HA on PEEK	HA/PEEK showed significantly higher BV, TbTh, TbN, bone density and BIC values when compared to uncoated PEEK	BIC was significantly more on both smooth and threaded sides of the HA/PEEK implant than uncoated PEEK (19.5 ± 14.5 % and 6 ± 6.1 %, respectively)	µCT Histomorphometry	N/A	Smooth and on side threaded  uncoated PEEK

Study	Model/duration	Type of modification	Finding/outcome	BIC	Evaluation method	Mechanical test	Implant design/ comparator
Tsou *et al.*, 2015	Rabbit femur 4, 8 and 12 weeks	TiO_2 coating with anatase phase (A-TiO_2/PEEK) and rutile phase (R-TiO_2/PEEK)	Good new bone formed on the coated implants showing progressive bone maturation. No direct bone contact on uncoated PEEK	R-TiO_2/PEEK demonstrated significantly more BIC than the other implants	Histology Push-out	Shear strength between implant and bone increased with time. At 12 weeks PEEK: 2.54 MPa A-TiO_2/PEEK: 3.02 MPa R-TiO_2/PEEK: 6.51 MPa Failure mode showed complete peeling of new bone on the uncoated PEEK, indicating poor osseointegration. R-TiO_2/PEEK showed many bone residuals on the implant surface, confirming excellent osteointegration	Smooth  uncoated PEEK
Deng *et al.*, 2015 a	Beagle dog, immediate implants after bilateral maxillary and mandibular rear molars of canines' extraction 4 and 12 weeks	n-HA/CRF-PEEK composite PEEK: 55 wt % n-HA: 25 wt % CRF: 20 wt %	n-HA/CRF-PEEK showed more bone formation than pure PEEK with continuous contact with the implant. BT/TV, TbN and TbTh values for n-HA/CRF-PEEK were significantly higher than for PEEK at both time points. A similar finding was found for bone labelling	n-HA/CRF-PEEK showed significantly more BIC than PEEK: 44.76 ± 4.25 % and 16.12 ± 2.43 %, respectively	µCT Histology Histomorphometry Bone labelling	N/A	Screw/thread  unmodified PEEK
Deng *et al.*, 2015b	Beagle dog, immediate implants after bilateral 3rd and 4th mandibular premolar extraction 8 weeks	n-HA/CRF-PEEK composite PEEK: 55 wt % n-HA: 25 % CRF: 20 wt % followed by sandblast with Al_2O_3 particles	Microroughened n-HA/CRF-PEEK showed more bone formation than smooth n-HA/CRF-PEEK with continuous contact with the implant. BT/TV, TbN, TbTh and BMD values for n-HA/CRF-PEEK were significantly higher than for control. Bone labelling percentage was significantly higher for the microroughened group as compared to the control	The microroughened n-HA/CRF-PEEK showed significantly larger BIC than the control	µCT Histology Histomorphometry Bone labelling	N/A	Screw/thread  un-sandblast n-HA/ CRF-PEEK composite

Study	Model/duration	Type of modification	Finding/outcome	BIC	Evaluation method	Mechanical test	Implant design/ comparator
Stübinger *et al.*, 2015	Sheep iliac model 2 and 12 weeks	Comparative study for different roughness plasma-sprayed Ti and HA coating on PEEK and CRF/PEEK. Control 1: PEEK Control 2: CRF/PEEK Coating A: low roughness Ti-coated PEEK Coating B: medium roughness Ti-coated CRF/PEEK Coating C: high roughness Ti-coated CRF/PEEK Coating D: double-coated CRF/PEEK	Noncalcified tissue around all types of implants was found at 2 weeks. At 12 weeks, a radiodense band was found without any sign of fibrous healing around the implants. Bone biomarkers did not show significant difference among the groups. Cancellous bone demonstrated more deposition of bone markers when compared to cortical bone	BIC showed overall increased values for all groups from 2 to 12 weeks, without statistically significant difference. Coating D revealed statistically more cancellous BIC than coating C and control 2 at 12 weeks BIC at 2 weeks Control 1: 39 ± 12 % Control 2: 26 ± 20 % Coating A: 26 ± 10 % Coating B: 8 ± 5 % Coating C: 11 ± 10 % Coating D: 10 ± 1 % BIC at 12 weeks Control 1: 67 ± 2 % Control 2: 22 ± 12 % Coating A: 59 ± 20 % Coating B: 59 ± 17 % Coating C: 36 ± 11 % Coating D: 69 ± 23 %	Microradiography Histology Histomorphometry Bone labelling Pull-out	Coating D demonstrated the highest pull-out values at both time points when compared to the other groups. Coating A, B, C and D showed statistically significant higher values at 12 weeks than the two controls. At 2 weeks Control 1: 28 ± 24 N Control 2: 50 ± 40 N Coating A: 230 ± 80 N Coating B: 330 ± 110 N Coating C: 125 ± 110 N Coating D: 370 ± 90 N At 12 weeks Control 1: 30 ± 20 N Control 2: 39 ± 24 N Coating A: 820 ± 200 N Coating B: 1180 ± 330 N Coating C: 930 ± 240 N Coating D: 1250 ± 270 N	Smooth  uncoated machine surface, both PEEK and CRF/PEEK
Walsh *et al.*, 2016	Sheep tibia, femur and spine fusion 4 and 12 weeks, tibia and femur 6, 12 and 26 weeks, spine	HA/PEEK-dispersed composite	HA/PEEK showed more bone formation than PEEK alone	Direct bone formation on HA/PEEK while fibrous healing on PEEK at 4 and 12 weeks was confirmed. HA/PEEK improved the spine fusion more than PEEK alone	µCT Histology	N/A	Smooth  unmodified PEEK
Durham *et al.*, 2016	Rabbit femoral condyle 6 and 18 weeks	Two-layer coating involving HA and YSZ on PEEK using two different heat processing: AD + MW and AD + MW + AC	The BV of AD + MW + AC group was significantly larger throughout the study than in uncoated PEEK. Both BV and RBMD demonstrated a higher trend on coated PEEK at 6 and 18 weeks when compared to uncoated PEEK	AD + MW showed a trend for more BIC than the other groups at 6 weeks, while at 18 weeks both coated PEEK showed a higher trend for BIC when compared to uncoated PEEK. No statistically significant differences were found between the BAR of the three groups at 6 and 18 weeks. However, at 6 weeks, a higher trend was observed for BAR than at 18 weeks	µCT Histology Bone labelling Pull-out	AD + MW + AC showed significantly more interfacial stiffness when compared to PEEK at 18 weeks. Pull-out values at 18 weeks showed a higher trend when compared to 6-week values	Smooth  uncoated PEEK

Study	Model/duration	Type of modification	Finding/outcome	BIC	Evaluation method	Mechanical test	Implant design/ comparator
Guillot *et al.*, 2016	Rabbit femoral condyle 4 and 8 weeks	Multilayer film of polyelectrolyte coating loaded with 9.3 µg of BMP-2 on PEEK and Ti implants	Direct new bone formation was observed on uncoated Ti and PEEK implants while osseo-gaps were observed in BMP-2-coated implants. Clear signs of bone loss were observed in coated implants, indicating an adverse effect of a high BMP-2 dose	BIC and BA values of uncoated implants were significantly higher than for BMP-2-coated implants	µCT Histomorphometry	N/A	Screw/thread  uncoated PEEK and Ti
Zhao *et al.*, 2016	Rat femur 8 weeks	Plasma immersion ion implantation (PIII) with H_2O (H_2OPIII) or ammonia (NH_3PIII)	Significantly more bone volume on modified PEEK after 1 and 2 weeks when compared to uncoated PEEK. After 1 week, the BV of H_2OPIII was 90 % and NH_3PIII 59 % more than control. This trend was increased until the 2nd week, then maintained till the end of the 8th week	PEEK: 36.5 % H_2OPIII: 46.4 % NH_3PIII: 48.5 %	µCT Histomorphometry Nanoindentation test	Elastic modulus of newly formed bone using nanoindentation. Modified surfaces demonstrated significantly higher values than unmodified PEEK, indicating more mineralisation PEEK: 6.8 ± 2.3 GPa H_2OPIII: 9.5 ± 2 GPa NH_3PIII: 8.5 ± 1 GPa	Smooth  unmodified PEEK
Johansson *et al.*, 2016	Rabbit femur 3 and 12 weeks	n-HA coating	Woven bone close to the implant and deeper lamellar bone were found. Haversian system observed within the threads of HA implants at 12 weeks	At 3 and 12 weeks, BIC value of HA/PEEK was statistically higher than uncoated PEEK at 3 weeks (14.1 ± 3.5 % and 11.1 ± 3.5 %, respectively) and 12 weeks (16.65 ± 6.7 % and 11.39 ± 3.8 %, respectively). BA of HA/PEEK and uncoated PEEK was 27.68 % and 25.04 % at 3 weeks while 49.66 % and 44.48 % at 12 weeks. BA inside the hole was significantly larger for HA/PEEK than uncoated PEEK at both 3 (17.21 % and 4.52 %, respectively) and 12 weeks (21.33 % and 10.80 %, respectively)	Histomorphometry	N/A	Screw/thread  uncoated PEEK

Study	Model/duration	Type of modification	Finding/outcome	BIC	Evaluation method	Mechanical test	Implant design/ comparator
Ouyang *et al.*, 2016	Rat femur (*Staphylococcus aureus*) 8 weeks	PEEK sulphonation by sulphuric acid followed by hydrothermal treatment (25 and 120 °C) for removal of acid residuals (SPW25 and SPW120)	Smaller sulphur contents of SPW120 showed good antibacterial ability with accentuated bone formation	SPW120 showed direct bone formation and high BIC value in both histological and μCT evaluation	μCT Histology	N/A	Smooth  unmodified PEEK
Ma *et al.*, 2016	Rabbits cranial defect 4 and 8 weeks	Biocomposite formation of n-CS/PEEK and n-HA/PEEK using compound and injection moulding	Both biocomposites promoted better osseointegration than PEEK. n-CS/PEEK showed significantly more new bone volume, bone biomarkers and BIC than control and n-HA/PEEK. SEM revealed gaps between bone and PEEK, indicating poor osseointegration	BIC value of n-CS/PEEK was significantly higher than the one of PEEK and n-HA/PEEK at both time points. A fibrous band was formed around PEEK at 4 and 8 weeks	μCT Histology SEM Bone labelling	N/A	Smooth  unmodified PEEK
Johansson *et al.*, 2017	Rabbit tibia and femur 20 weeks	Nano-thick and size HA spin coating (HA/PEEK)	μCT showed no statistically significant difference between groups. Both groups showed intimate contact between PEEK and bone, as measured histologically	High BIC and BA values were found without a statistically significant difference with uncoated PEEK	μCT Histomorphometry Torque removal test	HA/PEEK showed significantly higher values for removal torque than uncoated PEEK (6.42 ± 3.32 Ncm and 4.04 ± 1.39 Ncm, respectively)	Screw/thread  uncoated PEEK
Chen *et al.*, 2017	Rat calvaria (*Porphyromonas gingivalis*) 8 weeks	Fluorinated PEEK by plasma immersion ion implantation (PIII) followed by hydrofluoric acid treatment (A-F/PEEK)	Fibrous tissue encapsulating the uncoated PEEK was found, while direct bone formation was confirmed on A-F/PEEK. The modified surface showed bacteriostatic activity *in vitro*	A-F/PEEK showed significantly larger bone biomarkers percentage when compared to unmodified PEEK	μCT Histomorphometry Bone labelling	N/A	Smooth  uncoated PEEK

Study	Model/duration	Type of modification	Finding/outcome	BIC	Evaluation method	Mechanical test	Implant design/ comparator
Yang *et al.*, 2017	Dog mandible (periimplantitis model) 8 weeks	n-HA PEEK composite coating for SLA implant	Untied groups showed less bone resorption than tied groups. Implant-bone interface in the untied groups showed new bone formed directly on the implant surface	SLA-tied group showed lower BIC values than the n-HA-PEEK/SLA-tied group. n-HA-PEEK/SLA untied group demonstrated significantly higher MAR, BIC and shear strength values than both tied groups. BIC in SLA untied, n-HA-PEEK/SLA untied, SLA tied and n-HA-PEEK/SLA tied was 76.98 %, 78.82 %, 58.35 % and 67.98 %, respectively	Histology Bone labelling Pull-out	The maximum shear strength in SLA untied, n-HA-PEEK/SLA untied, SLA tied and n-HA-PEEK/SLA tied was 3.45 ± 0.33 MPa, 3.62 ± 0.1 MPa, 1.75 ± 0.1 MPa and 2.19 ± 0.2 MPa, respectively	Screw/thread  SLA untied n-HA-PEEK/ SLA untied
Ahn *et al.*, 2018	Rat tibia 8 weeks	PPP and PEEK smooth and porous implant designs	More bone formation revealed on PPP than PEEK	Porous PPP showed significantly more bone formation: 40 % increase of bone volume as compared to smooth PPP and PEEK	µCT Histology Finite element Push-out	50 % higher interface strength was found in porous PPP than PEEK	Solid and porous  PEEK
Yan *et al.*, 2018	Rabbit femoral condyle 4, 8 and 12 weeks	Graphene modification of CRF PEEK (G-CRF-PEEK) surface	G-CRF-PEEK showed significantly higher BV/TV and TbTh values than CRF-PEEK at 4 and 8 weeks only	Significantly more soft tissue between CRF-PEEK and bone. At 4 weeks BA and BIC values were significantly higher for G-CRF-PEEK (30.1 ± 1.7 % and 74.7 ± 4.7 %, respectively) than for CRF-PEEK (23.1 ± 1.9 % and 63.3 ± 6.5 %, respectively). At 8 weeks BA and BIC values were significantly higher for G-CRF-PEEK (31.9 ± 2.0 % and 83.6 ± 5.3 %, respectively) and for CRF-PEEK (27.3 ± 3.3 % and 73.8 ± 7.2 %, respectively)	µCT Histology Bone labelling Push-out	Maximum failure load of G-CRF-PEEK was significantly higher than that of CRF-PEEK at 4 and 8 weeks (3.37 ± 0.11 *vs.* 2.33 ± 0.1 MPa and 3.92 ± 0.18 *vs.* 3.25 ± 0.09 MPa, respectively)	Smooth  CRF-PEEK
Hassan *et al.*, 2018	Rabbit tibia 2 and 6 weeks	Nitrogen plasma treatment for PEEK (N_2PEEK)	New BA for N_2PEEK was significantly larger than for PEEK and Ti implants at 2 weeks. After 6 weeks, the N_2PEEK showed significantly higher value when compared to PEEK. At both time points, Ti implants showed significantly higher values than PEEK	N/A	Histology Histomorphometry Torque removal test	Plasma-treated PEEK showed significantly higher values when compared to Ti and PEEK at 2 weeks (3.97, 2.5 and 1.43 Ncm, respectively). While at 6 weeks, both Ti and plasma-treated PEEK showed significantly higher values when compared to PEEK (9.03, 9.16 and 5.87 Ncm, respectively)	Screw/thread  unmodified PEEK and Ti

Study characteristics

Studying the literature showed that various techniques had been applied to improve the bioactivity of PEEK implants. These include surface modification through chemical or physical treatment, surface coating with bioactive materials or implant composites with bioactive fillers. Fig. 3 shows the scheme of current strategies being used to modify the bioactivity of PEEK implants. Methods used to modify PEEK are listed in Table 3.

Pure PEEK implants

Osseointegration of unmodified PEEK implants was evaluated in comparison with other types of implants. Pure PEEK showed lesser BIC when compared to titanium. Koch *et al.* (2009) evaluated the osseointegration of zirconia in comparison to titanium after 4 months of healing. Histological evaluation showed a significantly lower level of BIC around PEEK implants when compared to titanium. Additionally, fibrous healing was found around PEEK implants (Koch *et al.*, 2009). A study in rat calvaria was conducted by Webster *et al.* (2012) to evaluate the anti-infective and osseointegration properties of silicon nitride, PEEK and titanium implants. PEEK demonstrated significantly low resistance to bacterial infection after incubation with *Staphylococcus epidermidis*, which led to compromised osseointegration (Webster *et al.*, 2012). Ahn *et al.* (2018) investigated the use of porous and solid poly[para-phenylene] (PPP) and PEEK implants. *In vivo* assessment was conducted to evaluate osseointegration. Solid implants of both materials showed a thin layer of bone yield on the implant surface, while the porous implants showed mineralised bone inside the pores and on the surface,

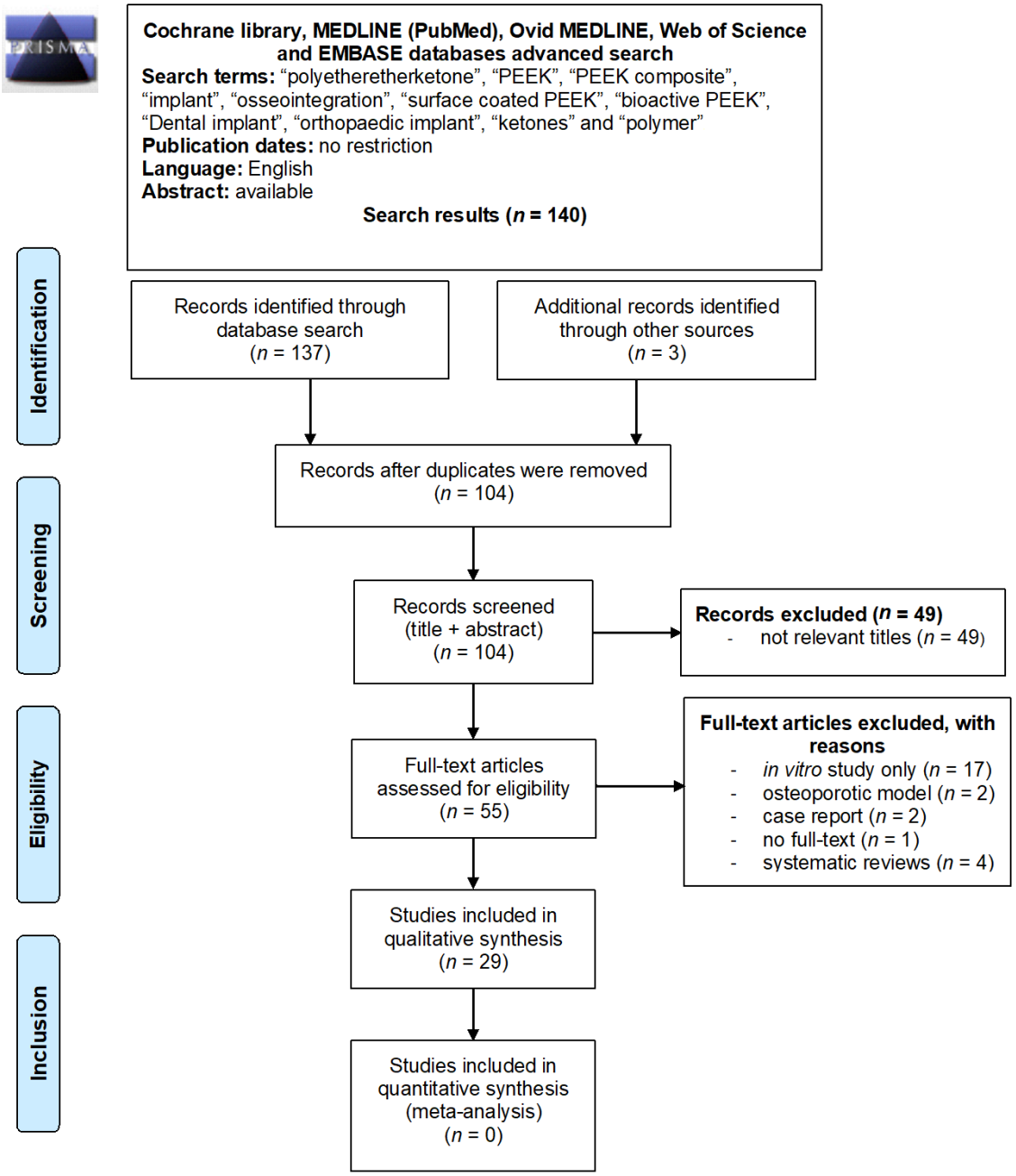


Fig. 2. Flow diagram of studies inclusion according to PRISMA guidelines.

Table 2. Quality assessment of the included studies (SYRCLE's RoB tool). Yes: low risk of bias; No: high risk of bias; ?: unknow risk of bias.

Study	Random sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding of personnel	Random outcome assessment	Blinding of outcomes assessment	Incomplete outcomes data	Selective reporting	Other bias
Koch *et al.*, 2009	?	?	?	?	?	?	?	?	?	Yes
Nakahara *et al.*, 2012	Yes	?	?	?	?	Yes	?	Yes	Yes	No
Barkarmo *et al.*, 2012	?	?	?	?	?	?	?	Yes	Yes	Yes
Webster *et al.*, 2012	Yes	?	?	?	?	?	Yes	Yes	Yes	Yes
Poulsson *et al.*, 2013	No	?	No	?	No	?	?	Yes	Yes	Yes
Xu *et al.*, 2014	?	?	?	?	?	?	?	?	?	Yes
Johansson *et al.*, 2014	?	?	?	?	?	?	?	Yes	Yes	?
Barkarmo *et al.*, 2014	?	?	?	?	?	?	?	Yes	Yes	Yes
Wang *et al.*, 2014	Yes	?	?	?	?	?	?	Yes	No	Yes
Lu *et al.*, 2015	Yes	?	?	?	?	Yes	?	Yes	Yes	Yes
Khoury *et al.*, 2015	?	?	?	?	?	?	?	Yes	Yes	Yes
Lee *et al.*, 2015	Yes	?	?	?	?	?	?	Yes	Yes	Yes
Tsou *et al.*, 2015	Yes	?	?	?	?	Yes	?	Yes	Yes	?
Deng *et al.*, 2015	?	?	?	?	?	?	?	Yes	Yes	Yes
Deng *et al.*, 2015	Yes	?	?	?	?	?	?	Yes	Yes	Yes
Stübinger *et al.*, 2015	?	?	?	?	?	?	?	Yes	Yes	Yes
Walsh *et al.*, 2016	?	?	?	?	?	?	?	Yes	Yes	Yes
Durham *et al.*, 2016	Yes	?	?	?	?	Yes	?	Yes	Yes	Yes
Guillot *et al.*, 2016	Yes	?	Yes	?	Yes	?	Yes	Yes	Yes	Yes
Zhao *et al.*, 2016	?	?	?	?	?	?	?	Yes	Yes	Yes
Johansson *et al.*, 2016	Yes	?	?	?	?	?	?	Yes	Yes	Yes
Ouyang *et al.*, 2016	No	?	?	?	?	?	?	Yes	Yes	Yes
Ma *et al.*, 2016	?	?	?	?	?	?	?	Yes	Yes	Yes
Johansson *et al.*, 2017	Yes	?	?	?	?	?	Yes	Yes	Yes	Yes
Chen *et al.*, 2017	?	?	?	?	?	?	?	Yes	Yes	Yes
Yang *et al.*, 2017	Yes	?	?	?	?	Yes	?	Yes	Yes	Yes
Ahn *et al.*, 2018	?	?	?	?	?	?	?	Yes	Yes	Yes
Yan *et al.*, 2017	?	?	?	?	?	?	?	Yes	Yes	Yes
Hassan *et al.*, 2017	No	?	No	?	No	?	?	Yes	Yes	Yes

as measured by micro-computed tomography (μCT) analysis. Porous PPP demonstrated higher osseointegration and bone volume as compared to the other implants. Similar findings were observed by histomorphometric analysis (Ahn *et al.*, 2018).

Surface-treated implants

The use of physical surface treatment to produce bioactive PEEK has been extensively studied. Khoury *et al.* (2015) functionalised PEEK using accelerated neutral atom beams (ANAB). This procedure produces a nanotextured surface topography without adding external material or changing the chemistry of PEEK. Khoury *et al.* (2015) successfully demonstrated a significant improvement in osseointegration of ANAB-treated implants by μCT, histomorphometric and push-out investigations.

Several plasma treatments have been applied to PEEK. Oxygen plasma has been analysed by Poulsson *et al.* (2013), with histological assessment and push-out testing. Compared with unmodified PEEK, the osseointegration of plasma-treated PEEK is significantly increased. Hassan *et al.* (2018) treated PEEK with nitrogen plasma. The results proved that this modification exhibits higher osseointegration when compared to untreated PEEK in histological and mechanical investigations.

Chemical surface treatment has also been utilised to modify the chemistry of PEEK surface. Ouyang *et al.* (2016) studied the effect of sulphonation using concentrated sulphuric acid on PEEK. They evaluated bone formation and antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*. The results revealed better osseointegration and antimicrobial ability on sulphonated PEEK than unmodified PEEK.

Coated implants

Various studies have assessed the efficacy of coating PEEK implants with bioactive materials to improve their osseointegration. Tsou *et al.* (2015) investigated whether anatase phase (A-TiO_2) or rutile phase (R-TiO_2) titanium could achieve better osseointegration. Both TiO_2 phases resulted in good bone formation on the implant surface. Importantly, R-TiO_2 showed significantly more BIC in histological assessment in addition to higher shear strength in mechanical tests. Based on these results, authors suggested that R-TiO_2 coating achieved better osseointegration (Tsou *et al.*, 2015). Stübinger *et al.* (2015) compared different roughness of titanium coatings and combined Ti/HA coating on PEEK and carbon-fibre-reinforced (CRF)/PEEK. The double coating showed the most favourable osseointegration (Stübinger *et al.*, 2015).

Several reports have shown that hydroxyapatite (HA) coating improves the osseointegration of PEEK implants (Barkarmo *et al.*, 2014; Barkarmo *et al.*, 2012; Durham *et al.*, 2016; Johansson *et al.*, 2014; Johansson *et al.*, 2016; Johansson *et al.*, 2017; Lee *et al.*, 2015; Nakahara *et al.*, 2012; Yang *et al.*, 2017). Lee *et al.* (2015) used cold-spray methods to apply a layer of micro-HA coating on PEEK. The results showed enhanced bone formation around the coated implants in histological and radiographical assessments (Lee *et al.*, 2015). Nakahara *et al.* (2012) evaluated the HA coating on CRF-PEEK. The results revealed a higher shear strength of the coated implants in comparison to the uncoated one (Nakahara *et al.*, 2012). This study showed more retention of HA-coated implants, which is in agreement with the studies by Johansson *et al.* (2014) and Barkarmo *et al.* (2014), who showed

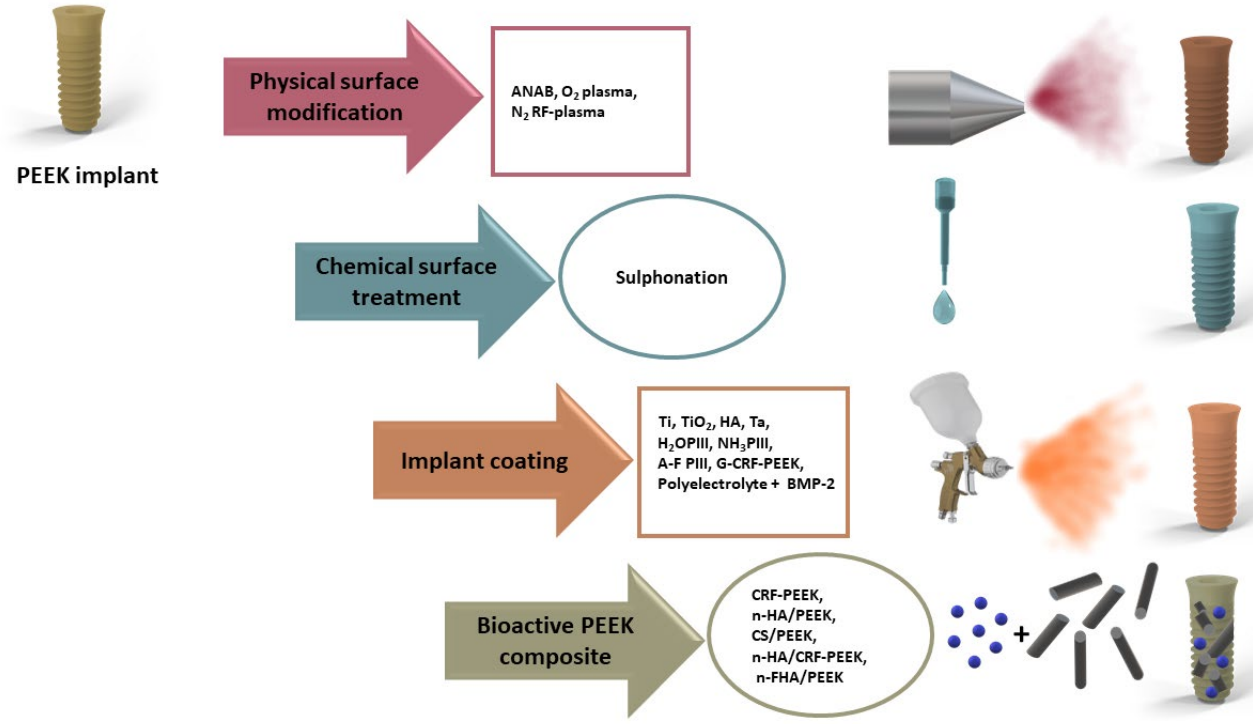


Fig. 3. The scheme of current strategies to modify the bioactivity of PEEK implants.

Table 3. Summary of methods used for PEEK modification.

Surface treatment	Coating	Bio composite
Chemical: • PEEK sulphonation **Physical:** • Nitrogen plasma (N_2PEEK) • Oxygen plasma (O_2PEEK) • Plasma immersion ion implantation (PIII) with H_2O (H_2OPIII) or ammonia (NH_3PIII) • ANAB • Porous design	• HA (HA/PEEK) through cold spray or spin coating (nano or micro scale) • Ti on PEEK (Ti/PEEK) • Ti on CRF/PEEK (Ti/CRF/PEEK) • HA on CRF/PEEK (HA/CRF/PEEK) • TiO_2/PEEK • Graphene coating (G-CRF-PEEK) • Silicate coating • Tantalum nanoparticles implantation by PIII • Fluorinated PEEK by PIII (A-F PIII/PEEK) • Two layers coating of HA and yttria-stabilised zirconia (YSZ) (HA/YSZ/PEEK) • Multilayer film of polyelectrolyte coating loaded with BMP-2	• CRF/PEEK • HA/PEEK • N-HA-CRF biocomposite + oxygen plasma ± TiO_2 blasting (PEEK/n-HA/CRF) • n-HA/CRF-PEEK composite ± plasma • n-FHA/PEEK • n-CS/PEEK

significantly higher removal torque values for nanohydroxyapatite (n-HA)-coated PEEK implants when compared to uncoated PEEK. Durham *et al.* (2016) added a thermal-insulating layer of yttria-stabilised zirconia to allow for crystallisation of the HA coating without damaging PEEK. μCT analysis, histological and mechanical evaluation confirmed more osseointegration in coated than uncoated implants.

Recent research has suggested that nano-sized particles of HA enhance osseointegration through mimicking cell-level n-HA (Ma and Tang, 2014). Barkarmo *et al.* (2012) investigated osseointegration of n-HA-coated PEEK. The results showed that 7 implants (38.9 %) failed to osseointegrate; 3 from the coated group and 4 from the control group. The smooth implant design and the lack of initial stability have been proposed as the leading causes of implant failure (Barkarmo *et al.*, 2012). In a different study, Barkarmo *et al.* (2014) investigated a threaded implant design using the same coating technique. This study demonstrated more implant stability and higher removal torque values when compared to uncoated implants. Johansson's research group investigated n-HA coating on PEEK (Johansson *et al.*, 2014; 2016; 2017). They comprehensively evaluated the n-HA coating histologically, radiographically and mechanically. These tests revealed that the n-HA-coated implant had significantly higher removal torque values, BIC ratio and BA than the uncoated PEEK. In addition to coating PEEK implants with various materials, HA/PEEK has been used to coat other implants. Yang *et al.* (2017) have investigated the effect of n-HA/PEEK coated on to sandblasted, large grit and acid-etched (SLA) titanium implants using a peri-implantitis model. The aim was to evaluate the effect of n-HA/PEEK coating on inflammatory cytokines and osseointegration. The authors concluded that coated SLA implants promoted better osseointegration and reduced inflammatory markers (Yang *et al.*, 2017).

Recently, researchers have shown an increased interest in deposition of a thin film to improve PEEK-bone interaction. Using plasma immersion ion implantation (PIII) technique, Lu *et al.* (2015) deposited tantalum on PEEK. Based on μCT, bone labelling and histological analysis, the application of tantalum for 30 min is associated with a significant increase in bone volume, percentage of bone labelling and BIC. Others have focused on the modification of PEEK by water and ammonia PIII (Zhao *et al.*, 2016). Overall, the *in vivo* results indicated that PIII implants stimulate bone formation at early stages.

Chen *et al.* (2017) introduced the incorporation of fluorine on to PEEK surfaces. Fluorinated PEEK demonstrated good osseointegration in an *in vivo* study. Importantly, it exhibited good bacteriostatic ability against *Porphyromonas gingivalis in vitro*. This would suggest that the fluorinated PEEK implants might be useful for dental applications (Chen *et al.*, 2017). Graphene coating has been applied on CRF-PEEK by Yan *et al.* (2018). It showed enhanced osseointegration through a significant increase in bone volume/tissue volume (BV/TV), trabecular thickness (TbTh), BIC and maximum failure load values *in vivo* (Yan *et al.*, 2018).

Bone morphogenic protein (BMP) coating on implants has been used to improve osseointegration.

Only one study by Guillot *et al.* (2016) evaluated the osseointegration of titanium and PEEK implants utilising a new BMP-2 delivery system that included polyelectrolyte multilayer films. In summary, the study by Guillot *et al.* (2016) showed that BMP-2-coated implants have lesser BIC and bone formation (Guillot *et al.*, 2016). The supraphysiological dose of BMP-2 could explain the results since BMP-2 can stimulate and/or inhibit both osteoblasts and osteoclasts, at different doses (James *et al.*, 2016). However, further studies are needed to specify the optimal dose of BMP-2 for implant coating.

Bioactive composite implants

The incorporation of PEEK with bioactive materials has been suggested to improve its osseointegration. Many bioactive composite combinations with pure PEEK have been proposed (Deng *et al.*, 2015a; Deng *et al.*, 2015b; Ma *et al.*, 2016; Walsh *et al.*, 2016; Wang *et al.*, 2014; Xu *et al.*, 2014). Furthermore, composites with carbon fibres to improve mechanical properties have been utilised in orthopaedic implants (Lee *et al.*, 2012; Schwitalla *et al.*, 2016). HA has been used as a bioactive filler with PEEK (Deng *et al.*, 2015a; Deng *et al.*, 2015b; Ma *et al.*, 2016; Wang *et al.*, 2014; Walsh *et al.*, 2016; Xu *et al.*, 2014).

Walsh *et al.* (2016) evaluated an HA/PEEK composite both radiographically and histologically. The composite showed more direct bone formation when compared to PEEK. Another manufacturing technique was proposed by Ma *et al.* (2016), who investigated the use of compound and injection moulding techniques of different bioceramic nanoparticles of silicate and HA to yield biocomposites. The study revealed that both composites nano-calcium silicate (n-CS)/PEEK and n-HA/PEEK enhanced osseointegration. Additionally, n-CS/PEEK demonstrated more BIC and bone formation than n-HA/PEEK and PEEK. Fibrous tissue was observed around the pure PEEK at 4 and 8 weeks postoperatively. These histological findings agreed with the observations of Koch *et al.* (2009), Durham *et al.* (2016) and Walsh *et al.* (2016), according to which bare PEEK shows fibrous formation around the implants. The authors concluded that n-CS/PEEK has a stronger capability for osseointegration.

On the other hand, obtaining PEEK composites reinforced with carbon fibre and enhanced by nano-sized bioactive materials including HA, fluorohydroxyapatite (FHA) and TiO_2 is a promising approach to improve both mechanical and bioactivity properties. Deng *et al.* (2015) prepared a n-HA/CRF-PEEK composite. The 2D histology and 3D μCT results showed improved bone regeneration around the composite implants when compared to pure PEEK implants (Deng *et al.*, 2015b). To improve the bone growth on the composite, some measures were adopted to prepare different roughness of the composite. Another study by Deng *et al.* (2015) investigated various microroughened implants using sandblasting with Al_2O_3 particles. The study showed that the n-HA/CRF/PEEK implants with micro-rough surfaces had improved bone regeneration around the implants when compared with smooth implants, as assessed by μCT and histological analysis (Deng *et al.*, 2015a). Thus, bioactive HA composites were considered to significantly improve the osseointegration of PEEK, especially with the combination of composites and modified roughness. Xu and co-workers (2014) produced a n-HA/CRF/PEEK composite with micro/nano topographical surface through TiO_2 blasting followed by oxygen plasma treatment. The authors showed that this approach permits more BIC and larger bone volume (Xu *et al.*, 2014).

The nano-FHA composite (n-FHA/PEEK) was tested. Wang *et al.* (2014) observed a significant increase in BIC around n-FHA/PEEK implants when compared with pure PEEK. More importantly, the n-FHA/PEEK implant showed an antimicrobial effect on *Streptococcus* mutants, which are considered to be the primary pathogens for periodontitis and implant failure (Wang *et al.*, 2014).

Discussion

The present literature review attempted to explore the available methods to improve the bioactivity of PEEK implants and optimise osseointegration. The search strategy was comprehensive, with no time restrictions and inclusion criteria were clearly specified in the prespecified PROSPERO protocol; therefore, the risk of biased selection of studies was minimal. The methodology of conducting the review was critically appraised to assess and avoid risk of bias using AMSTAR 2 instrument and ROBIS tool. Whether PEEK could be used as a dental implant remains a topic to be investigated. All previously described animal studies revealed better bone growth on to the modified PEEK as compared to non-modified PEEK surfaces. There are no valid scientific data available to recommend the routine clinical use of PEEK implants in the oral cavity, with a questionable quality of the clinical studies available. Only two studies have attempted to use PEEK implants in the human mouth; both studies were case reports with a limited number of participants and short-term follow-up (Khonsari *et al.*, 2014; Marya *et al.*, 2011). There are several animal models that have been considered to test the osseointegration of PEEK implants, including rats, rabbits, dogs, sheep and pigs. Moreover, the anatomical location and type of bone where these implants were inserted was not standardised. Only six studies evaluated the osseointegration of PEEK implants in the jaw bones of dogs.

The implant design would affect its osseointegration, which was clearly shown in the two studies by Barkarmo *et al.* (2012, 2014), where the high failure rate was associated with the smooth

designs. Successful dental implants should withstand the forces of mastication. Results from *in vitro* and *in vivo* studies are deficient in determining the osseointegration of PEEK implants in the clinical scenario because not all the implants were loaded (Najeeb *et al.*, 2016). Therefore, future studies are recommended to provide more insight into the stability of the implants when they are subjected to masticatory forces.

The studies included in the present review showed several limitations. The inadequacies in the animal study designs and the absence of a predetermined sample size calculation could result in biased outcomes and conclusions. Only in one study (Guillot *et al.* 2016) was the risk of bias found to be low based on the quality assessment. Three studies (Guillot *et al.*, 2016; Johansson *et al.*, 2017; Webster *et al.*, 2012) performed a blind assessment of the outcome. Most of the included studies demonstrated a high or unknown risk of bias during the quality assessment.

Baseline characteristics of the animal, allocation concealment, random housing, blinding of personnel and randomisation protocol were not described. These are crucial to improve the quality of the animal research and to minimise the risk of bias according to the recommendations of SYRCLE (Hooijmans *et al.*, 2014). No study to date has applied modified PEEK dental implants in humans. Therefore, the true clinical relevance of modified PEEK osseointegration remains unknown. However, as mentioned earlier, two papers were identified during the manual search that demonstrate clinical application of PEEK dental implants. Marya *et al.* (2011) presented three cases of PEEK dental implants. The implants were composed of 20 % beta-tricalcium phosphate and titanium oxide and 80 % PEEK. All the cases were loaded after 1 week. They concluded that PEEK implants had potential for osteointegration at 6 months follow-up without mentioning the method of assessment (Marya *et al.*, 2011). The rationale behind the conclusion of osseointegration was not clearly described. The findings of Marya *et al.* (2011) contrast with Khonsaria *et al.* (2014), who presented three cases of failed PEEK implants with severe infection and concluded that poor osseointegration led to implant loss.

To translate the use of PEEK implants to humans, preclinical evidence of satisfactory osseointegration and standardised outcome measures are still needed. Therefore, future preclinical studies should apply strict criteria related to the selection of the animal model to improve homogeneity of studies and analyses.

Conclusion

The review summarises the current strategies based on *in vivo* studies to improve the osseointegration of PEEK implants. The osseointegration of modified PEEK remains debatable. Currently, for the osseointegration of PEEK implants, several obstacles need to be addressed. First, the necessity for a single standard test identifying the minimum mechanical requirements for successful implant osseointegration. Crucially, this should incorporate various forms of mechanical assessment (including cyclic loading) with different engineering approaches to mimic the natural environment. The second obstacle is to address the inadequacy in the design of the animal studies. Furthermore, utilising the criteria for the SYRCLE's RoB tool as a reporting checklist would improve the quality of preclinical studies.

Due to varying animal models, experimental designs and methods of analysis used to address the osseointegration of PEEK implants in current experimental research, standardised designs to assess the implant osseointegration in experimental research are required. Furthermore, in many of these studies, there were limitations in reporting on the methodology, sample size calculation and statistical methods. Further research is required to provide more insight into the stability of the modified implants when they are subjected to cyclic loading to mimic the appropriate functional requirements. These are required to obtain enough evidence to enable the use of PEEK implants as an alternative implant for clinical cases.

Acknowledgements

The authors confirm that they have no conflicts of interest with any organisation regarding the material discussed in the review. The authors would like to thank Deanship of scientific research for supporting this research through the initiative of DSR Scholarship.

NA conducted the search protocol, extracted the data, assess the quality of the included studies. KN assess the quality of extracted data, analysis, interpretation and critically revised the manuscript. DC reviewed the manuscript and guided the systematic review. AA checked the accuracy of the data and critically revised the manuscript.

References

Ahn H, Patel RR, Hoyt AJ, Lin ASP, Torstrick FB, Guldberg RE, Frick CP, Carpenter RD, Yakacki CM, Willett NJ (2018) Biological evaluation and finite-element modeling of porous poly(para-phenylene) for orthopaedic implants. Acta Biomater **72**: 352-361.

Albrektsson T, Chrcanovic B, Jacobsson M, Wennerberg A (2017) Osseointegration of implants – a biological and clinical overview. JSM Dent Surg **2**: 1022.

Barkarmo S, Andersson M, Currie F, Kjellin P, Jimbo R, Johansson CB, Stenport V (2014) Enhanced bone healing around nanohydroxyapatite-coated polyetheretherketone implants: an experimental study in rabbit bone. J Biomater Appl **29**: 737-747.

Barkarmo S, Wennerberg A, Hoffman M, Kjellin P, Breding K, Handa P, Stenport V (2012) Nano-hydroxyapatite-coated PEEK implants: a pilot study in rabbit bone. J Biomed Mater Res Part A **101A**: 465-471.

Chen M, Ouyang L, Lu T, Wang H, Meng F, Yang Y, Ning C, Ma J, Liu X (2017) Enhanced bioactivity and bacteriostasis of surface fluorinated polyetheretherketone. ACS Appl Mater Interfaces **9**: 16824-16833.

Chien PFW, Khan KS, Siassakos D (2012) Registration of systematic reviews: PROSPERO. BJOG **119**: 903-905.

Cinderey MB, Rose JB (1979) Production of aromatic polyethers. Google Patents. US4176222A.

Deng Y, Liu X, Xu A, Wang L, Luo Z, Zheng Y, Deng F, Wei J, Tang Z, Wei S (2015a) Effect of surface roughness on osteogenesis *in vitro* and osseointegration *in vivo* of carbon fiber-reinforced polyetheretherketone-nanohydroxyapatite composite. Int J Nanomedicine **10**: 1425-1447.

Deng Y, Zhou P, Liu X, Wang L, Xiong X, Tang Z, Wei J, Wei S (2015b) Preparation, characterization, cellular response and *in vivo* osseointegration of polyetheretherketone/nano-hydroxyapatite/carbon fiber ternary biocomposite. Colloids Surf B Biointerfaces **136**: 64-73.

Durham JW, Montelongo SA, Ong JL, Guda T, Allen MJ, Rabiei A (2016) Hydroxyapatite coating on PEEK implants: biomechanical and histological study in a rabbit model. Mater Sci Eng C **68**: 723-731.

Elawadly T, Radi IAW, El Khadem A, Osman RB (2017) Can PEEK be an implant material? Evaluation of surface topography and wettability of filled *versus* unfilled PEEK with different surface roughness. J Oral Implantol **43**: 456-461.

Eschbach L (2000) Nonresorbable polymers in bone surgery. Injury **31**: D22-27.

Gao X, Fraulob M, Haïat G (2019) Biomechanical behaviours of the bone-implant interface: a review. J R Soc Interface **16**: 20190259. DOI: 10.1098/rsif.2019.0259.

Guillot R, Pignot-Paintrand I, Lavaud J, Decambron A, Bourgeois E, Josserand V, Logeart-Avramoglou D, Viguier E, Picart C (2016) Assessment of a polyelectrolyte multilayer film coating loaded with BMP-2 on titanium and PEEK implants in the rabbit femoral condyle. Acta Biomater **36**: 310-322.

Gupta S, Patil N, Solanki J, Singh R, Laller S (2015) Oral implant imaging: a review. Malaysian J Med Sci **22**: 7-17.

Hassan AH, Al-Judy HJ, Fatalla AA (2018) Biomechanical effect of nitrogen plasma treatment of polyetheretherketone dental implant in comparison to commercially pure titanium. J Res Med Dent Sci **6**: 367-377.

Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW (2014) SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol **14**: 43. DOI: 10.1186/1471-2288-14-43.

James AW, LaChaud G, Shen J, Asatrian G, Nguyen V, Zhang X, Ting K, Soo C (2016) A review of the clinical side effects of bone morphogenetic protein-2. Tissue Eng Part B Rev **22**: 284-297.

Johansson P, Barkarmo S, Hawthan M, Peruzzi N, Kjellin P, Wennerberg A (2017) Biomechanical, histological, and computed X-ray tomographic analyses of hydroxyapatite coated PEEK implants in an extended healing model in rabbit. J Biomed Mater Res Part A **106**: 1440-1447.

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

Johansson P, Jimbo R, Naito Y, Kjellin P, Currie F, Wennerberg A (2016) Polyether ether ketone implants achieve increased bone fusion when coated with nano-sized hydroxyapatite: a histomorphometric study in rabbit bone. Int J Nanomedicine **11**: 1435-1442.

Khonsari RH, Berthier P, Rouillon T, Perrin JP, Corre P (2014) Severe infectious complications after PEEK-derived implant placement: report of three cases. J Oral Maxillofac Surg Med Pathol **26**: 477-482.

Khoury J, Maxwell M, Cherian RE, Bachand J, Kurz AC, Walsh M, Assad M, Svrluga RC (2015) Enhanced bioactivity and osseointegration of PEEK with accelerated neutral atom beam technology. J Biomed Mater Res B Appl Biomater **105**: 531-543.

Kini U, Nandeesh BN (2012) Physiology of bone formation, remodeling, and metabolism. In: Radionuclide and hybrid bone imaging. Editors: Fogelman I, Gnanasegaran G, van der Wall H. Springer, Berlin, Heidelberg. pp: 29-57.

Koch FP, Weng D, Krämer S, Biesterfeld S, Jahn-Eimermacher A, Wagner W (2009) Osseointegration of one-piece zirconia implants compared with a titanium implant of identical design: a histomorphometric study in the dog. Clin Oral Implants Res **21**: 350-356.

Kurtz S (2012) PEEK Biomaterials Handbook. DOI: 10.1016/C2010-0-66334-6.

Lee JH, Jang HL, Lee KM, Baek HR, Jin K, Noh JH (2015) Cold-spray coating of hydroxyapatite on a three-dimensional polyetheretherketone implant and its biocompatibility evaluated by *in vitro* and *in vivo* minipig model. J Biomed Mater Res B Appl Biomater **105**: 647-57.

Lee WT, Koak JY, Lim YJ, Kim SK, Kwon HB, Kim MJ (2012) Stress shielding and fatigue limits of poly-ether-ether-ketone dental implants. J Biomed Mater Res B Appl Biomater **100B**: 1044-1052.

Lu T, Wen J, Qian S, Cao H, Ning C, Pan X, Jiang X, Liu X, Chu PK (2015) Enhanced osteointegration on tantalum-implanted polyetheretherketone surface with bone-like elastic modulus. Biomaterials **51**: 173-83.

Ma R, Tang T (2014) Current strategies to improve the bioactivity of PEEK. Int J Mol Sci **15**: 5426-5445.

Ma R, Yu Z, Tang S, Pan Y, Wei J, Tang T (2016) Osseointegration of nanohydroxyapatite- or nano-

calcium silicate-incorporated polyetheretherketone bioactive composites *in vivo*. Int J Nanomedicine **11**: 6023-6033.

Marya K, Dua J, Chawla S, Sonoo PR, Aggarwal A, Singh V (2011) Polyetheretherketone (PEEK) dental implants: a case for immediate loading. Int J Oral Implantol Clin Res **2**: 97-103.

Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ **21**: b2535. DOI: 10.1136/bmj.b2535.

Najeeb S, Khurshid Z, Zohaib S, Zafar MS (2016) Bioactivity and osseointegration of PEEK are inferior to those of titanium - a systematic review. J Oral Implantol **42**: 512-516.

Najeeb S, Zafar MS, Khurshid Z, Siddiqui F (2016) Applications of polyetheretherketone (PEEK) in oral implantology and prosthodontics. J Prosthodont Res **60**: 12-19.

Nakahara I, Takao M, Goto T, Ohtsuki C, Hibino S, Sugano N (2012) Interfacial shear strength of bioactive-coated carbon fiber reinforced polyetheretherketone after *in vivo* implantation. J Orthop Res **30**: 1618-1625.

Ouyang L, Zhao Y, Jin G, Lu T, Li J, Qiao Y, Ning C, Zhang X, Chu PK, Liu X (2016) Influence of sulfur content on bone formation and antibacterial ability of sulfonated PEEK. Biomaterials **83**: 115-126.

Poulsson AHC, Eglin D, Zeiter S, Camenisch K, Sprecher C, Agarwal Y, Nehrbass D, Wilson J, Richards RG (2013) Osseointegration of machined, injection moulded and oxygen plasma modified PEEK implants in a sheep model. Biomaterials **35**: 3717-3728.

Reinhardt B, Beikler T (2014) Dental implants. In: Advanced ceramic for dentistry. Editors: Shen JZ, Kosmac T. Elsevier, Waltman, MA, USA. pp: 51-75. DOI:10.1016/B978-0-12-394619-5.00004-3.

Schwitalla AD, Spintig T, Kallage I, Müller WD (2016) Pressure behavior of different PEEK materials for dental implants. J Mech Behav Biomed Mater **54**: 295-304.

Schwitalla A, Müller W-D (2013) PEEK Dental implants: a review of the literature. J Oral Implantol **39**: 743-749.

Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA (2017) AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ **358**: j4008. DOI: 10.1136/bmj.j4008.

Shibata Y, Tanimoto Y, Maruyama N, Nagakura M (2015) A review of improved fixation methods for dental implants. Part II: biomechanical integrity at bone-implant interface. J Prosthodont Res **59**: 84-95.

Sicilia A, Cuesta S, Coma G, Arregui I, Guisasola C, Ruiz E, Maestro A (2008) Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients. Clin Oral Implants Res. **19**: 823-835.

Sidambe AT (2014) Biocompatibility of advanced manufactured titanium implants-a review. Materials (Basel) **7**: 8168-8188.

Skirbutis G, Dzingutė A, Masiliūnaitė V, Šulcaitė G, Žilinskas J (2017) A review of PEEK polymer's properties and its use in prosthodontics. Stomatologija **19**: 19-23.

Stübinger S, Drechsler A, Bürki A, Klein K, Kronen P, von Rechenberg B (2015) Titanium and hydroxyapatite coating of polyetheretherketone and carbon fiber-reinforced polyetheretherketone: a pilot study in sheep. J Biomed Mater Res B Appl Biomater **104**: 1182-1191.

Tsou HK, Chi MH, Hung YW, Chung CJ, He JL (2015) *In vivo* osseointegration performance of titanium dioxide coating modified polyetheretherketone using arc ion plating for spinal implant application. Biomed Res Int **2015**: 328943. DOI: 10.1155/2015/328943.

Volpe S, Verrocchi D, Andersson P, Gottlow J, Sennerby L (2008) Comparison of early bacterial colonization of PEEK and titanium healing abutments using real-time PCR. Appl Osseointegration Res **6**: 54-62.

Walsh WR, Pelletier MH, Bertollo N, Christou C, Tan C (2016) Does PEEK/HA enhance bone formation compared with PEEK in a sheep cervical fusion model? Clin Orthop Relat Res **474**: 2364-2372.

Wang L, He S, Wu X, Liang S, Mu Z, Wei J, Deng F, Deng Y, Wei S (2014) Polyetheretherketone/nano-fluorohydroxyapatite composite with antimicrobial activity and osseointegration properties. Biomaterials **35**: 6758-75.

Webster TJ, Patel AA, Rahaman MN, Sonny Bal B (2012) Anti-infective and osteointegration properties of silicon nitride, poly(ether ether ketone), and titanium implants. Acta Biomater **8**: 4447-4454.

Xu A, Liu X, Gao X, Deng F, Deng Y, Wei S (2014) Enhancement of osteogenesis on micro/nano-topographical carbon fiber-reinforced polyetheretherketone-nanohydroxyapatite biocomposite. Mater Sci Eng C **48**: 592-528.

Yan JH, Wang CH, Li KW, Zhang Q, Yang M, Di-Wu WL, Yan M, Song Y, Ba JJ, Bi L, Han YS (2018) Enhancement of surface bioactivity on carbon fiber-reinforced polyether ether ketone *via* graphene modification. Int J Nanomedicine **13**: 3425-3440.

Yang H-W, Tang X-S, Tian Z-W, Wang Y, Yang W-Y, Hu J-Z (2017) Retracted: effects of nano-hydroxyapatite/polyetheretherketone-coated, sandblasted, large-grit, and acid-etched implants on inflammatory cytokines and osseointegration in a peri-implantitis model in beagle dogs. Med Sci Monit **23**: 4601. DOI: 10.12659/msm.914241.

Zarb GA, Albrektsson T (1991) Osseointegration: a requiem for the periodontal ligament. Int J Periodontics Restor Dent **11**: 88-91.

Zhao Y, Wong HM, Lui SC, Chong EYW, Wu G, Zhao X, Wang C, Pan H, Cheung KMC, Wu S, Chu PK, Yeung KWK (2016) Plasma surface functionalized polyetheretherketone for enhanced osseo-integration at bone-implant interface. ACS Appl Mater Interfaces **8**: 3901-3911.

Zivic F, Affatato S, Trajanovic M, Schnabelrauch M, Grujovic N, Choy KL (2017) Biomaterials in

clinical practice. Advances in clinical research and medical devices. Springer International Publishing. DOI: 10.1007/978-3-319-68025-5.

Web References

1. http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018116061 [24.06.2019]

2. https://www.bristol.ac.uk/media-library/sites/social-community-medicine/robis/robisguidancedocument.pdf [28.03.2018]

Editor's note: All comments/questions by the reviewers were answered by making changes in the text. Hence, there is no Discussion with Reviewers section.

The Scientific Editor responsible for this paper was Thimios Mitsiadis.