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

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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.

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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 (Cinderley 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 (Albrektsson et al., 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 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.

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 healthy 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:

![Fig. 1. PEEK chemical formula.](www.ecmjournal.org)
• 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); TiO₂: titanium dioxide; ANAB: accelerated neutral atom beam; SEM: scanning electron microscopy; µCT: micro-computed tomography.
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<tr>
<th>Study</th>
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<tr>
<td>Koch et al., 2009</td>
<td>Dog split mouth model 4 months</td>
<td>A comparative study between different implants including uncoated zirconia, calcium-</td>
<td>All implants were osseointegrated clinically and histologically</td>
<td>PEEK: 26.8 %  Ti: 41.2 %</td>
<td>Histomorphometry</td>
<td>N/A</td>
<td>Screw/thread</td>
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<td>liberating TiO&lt;sub&gt;2&lt;/sub&gt;-coated zirconia, Ti implant and PEEK</td>
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<td>Uncoated zirconia: 59.2 %  Coated zirconia: 58.3 %  Connective tissue was found around PEEK implant</td>
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<tr>
<td>Nakahara et al., 2012</td>
<td>Rabbit femur 6 and 12 weeks</td>
<td>HA coating for CRF-PEEK and Ti</td>
<td>Direct bone formation on coated implants that increased in time</td>
<td>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</td>
<td>Histology</td>
<td>Pull-out</td>
<td>Smooth CRF-PEEK and Ti</td>
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<tr>
<td>Barkarmo et al., 2012</td>
<td>Rabbit femur 6 weeks</td>
<td>n-HA spin coating</td>
<td>7 implants failed; 3 of them were coated implants</td>
<td>Histology</td>
<td>Histomorphometry</td>
<td>N/A</td>
<td>Smooth PEEK</td>
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<td>Webster et al., 2012</td>
<td>Rat calvaria bacteria-induced</td>
<td>No-modification comprehensive study to evaluate the anti-infective and osseointegration properties of SN, PEEK and Ti</td>
<td>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: 49 %  Live bacteria around PEEK were 88 %, around Ti 21 % and none adjacent to SN</td>
<td>BIC values at 90 d  without bacterial injection: PEEK: 8 %  Ti: 19 %  SN: 59 %  with bacterial injection: PEEK: 5 %  Ti: 9 %  SN: 23 %</td>
<td>Histomorphometry</td>
<td>Push out</td>
<td>Smooth no bacterial injection</td>
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(Staphylococcus epidemidiosis) 3, 7, 14 and 90 d
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<tr>
<td>Poulsson et al., 2014</td>
<td>Sheep tibia and femur 4, 12 and 26 weeks</td>
<td>Oxygen plasma treatment on moulded and machined PEEK OPTIMA (well known medical grade PEEK)</td>
<td>Microroughness by machined process had significantly enhanced BIC and push-out values at all time points</td>
<td>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</td>
<td>Histology</td>
<td>Bone labelling</td>
<td>Push-out</td>
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<td>Xu et al., 2014</td>
<td>Beagle dog; immediate implant after mandibular premolar extraction 4 weeks</td>
<td>n-HA biocomposite (PEEK/n-HA/CRF) HA: 25 wt % CRF: 15 wt % PEEK: 60 wt % followed by TiO₂ blasting with oxygen plasma treatment (p-m-PEEK/n-HA/CRF) or only oxygen plasma treatment (p-PEEK/n-HA/CRF)</td>
<td>p-m-PEEK/n-HA/CRF showed a significantly more BV/TV and TbTh than the other groups</td>
<td>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</td>
<td>μCT</td>
<td>Histology</td>
<td>Bone labelling</td>
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<td>Johansson et al., 2014</td>
<td>Rabbit tibia 3 and 12 weeks</td>
<td>n-HA coating</td>
<td>N/A</td>
<td>N/A</td>
<td>Removal torque test</td>
<td>HA-coated PEEK showed significantly higher removal torque values after both healing periods</td>
<td>Screw/thread</td>
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<tr>
<td>Barkarmo et al., 2014</td>
<td>Rabbit tibia and femur 6 weeks</td>
<td>n-HA coating</td>
<td>Coated implant revealed more bone formation when compared to uncoated one</td>
<td>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</td>
<td>Histomorphometry (femur)</td>
<td>Removal torque test (tibia)</td>
<td>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)</td>
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<td>Wang et al., 2014</td>
<td>Beagle dog, immediate implant after 3rd and 4th mandibular premolar extraction (in vitro Staphylococcus mutans)</td>
<td>n-FHA/PEEK composite n-FHA: 40 wt % PEEK: 60 wt %</td>
<td>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</td>
<td>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</td>
<td>µCT</td>
<td>Histology</td>
<td>Push-out</td>
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<td>Lu et al., 2015</td>
<td>Rat femur, 8 weeks</td>
<td>Tantalum nanoparticles implantation by plasma immersion ion implantation (PIII) for 30 min (Ta-30) and 120 min (Ta-120)</td>
<td>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</td>
<td>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 %)</td>
<td>µCT</td>
<td>Histology</td>
<td>µCT</td>
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<td>Khoury et al., 2015</td>
<td>Sheep hind limb, bilaterally 4 and 12 weeks</td>
<td>PEEK surface modified by ANAB</td>
<td>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</td>
<td>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</td>
<td>µCT</td>
<td>Histomorphometry</td>
<td>Push-out</td>
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<td>Lee et al., 2015</td>
<td>Minipig iliac and intervertebral cage (spine model) 8 weeks</td>
<td>Cold spray of HA on PEEK</td>
<td>HA/PEEK showed significantly higher BV, TbTh, TbN, bone density, and BIC values when compared to uncoated PEEK</td>
<td>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)</td>
<td>µCT</td>
<td>Histomorphometry</td>
<td>N/A</td>
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<td>Tsou et al., 2015</td>
<td>Rabbit femur</td>
<td>TiO₂ coating with anatase phase (A-TiO₂/PEEK) and rutile phase (R-TiO₂/PEEK)</td>
<td>Good new bone formed on the coated implants showing progressive bone maturation. No direct bone contact on uncoated PEEK</td>
<td>R-TiO₂/PEEK demonstrated significantly more BIC than the other implants</td>
<td>Histology</td>
<td>Shear strength between implant and bone increased with time.</td>
<td>Smooth</td>
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<td></td>
<td>4, 8 and 12 weeks</td>
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<td>At 12 weeks PEEK: 2.54 MPa A-TiO₂/PEEK: 3.02 MPa R-TiO₂/PEEK: 6.51 MPa</td>
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<td>Failure mode showed complete peeling of new bone on the uncoated PEEK, indicating poor osseointegration. R-TiO₂/PEEK showed many bone residuals on the implant surface, confirming excellent osteointegration</td>
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<td>Deng et al., 2015 a</td>
<td>Beagle dog, immediate implants after bilateral maxillary and mandibular rear molars of canines’ extraction</td>
<td>n-HA/CRF-PEEK composite PEEK: 55 wt % n-HA: 25 wt % CRF: 20 wt %</td>
<td>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</td>
<td>n-HA/CRF-PEEK showed significantly more BIC than PEEK: 44.76 ± 4.25 % and 16.12 ± 2.43 %, respectively</td>
<td>µCT</td>
<td>Bone labelling percentage was significantly higher for the microroughened group as compared to the control</td>
<td>Screw/thread unmodified PEEK</td>
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<tr>
<td>Deng et al., 2015 b</td>
<td>Beagle dog, immediate implants after bilateral 3rd and 4th mandibular premolar extraction</td>
<td>n-HA/CRF-PEEK composite PEEK: 55 wt % n-HA: 25 % CRF: 20 wt % followed by sandblast with Al₂O₃ particles</td>
<td>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</td>
<td>The microroughened n-HA/CRF-PEEK showed significantly larger BIC than the control</td>
<td>µCT</td>
<td>Bone labelling</td>
<td>Screw/thread un-sandblast n-HA/CRF-PEEK composite</td>
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<td>Stübinger et al., 2015</td>
<td>Sheep iliac model 2 and 12 weeks</td>
<td>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</td>
<td>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</td>
<td>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</td>
<td>Microradiography Histology Histomorphometry Bone labelling Pull-out</td>
<td>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.</td>
<td>Smooth uncoated machine surface, both PEEK and CRF/PEEK</td>
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<td>Walsh et al., 2016</td>
<td>Sheep tibia, femur and spine fusion 4 and 12 weeks, tibia and femur 6, 12 and 26 weeks, spine</td>
<td>HA/PEEK-dispersed composite</td>
<td>HA/PEEK showed more bone formation than PEEK alone</td>
<td>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</td>
<td>µCT Histology</td>
<td>N/A</td>
<td>Smooth unmodified PEEK</td>
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<td>Durham et al., 2016</td>
<td>Rabbit femoral condyle 6 and 18 weeks</td>
<td>Two-layer coating involving HA and YSZ on PEEK using two different heat processing: AD + MW and AD + MW + AC</td>
<td>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</td>
<td>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</td>
<td>µCT Histology Bone labelling Pull-out</td>
<td>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</td>
<td>Smooth uncoated PEEK</td>
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Implant design

Stud highest pull-out values at both without statistically significant other groups. Coating A, B, C and Noncalcified tissueComparative study for different around all types of statistically more cancellous BIC than roughness plasma-sprayed Ti implants was found at CRF/PEEK.

Microradiography a radiodense band was BIC at 2 weeks Control 1: 39% Bone biomarkers did not show significant Control 2: 50% and 12 weeks Coating A: 26% Coating B: 59% ± % Coating C: 11% Coating D: 10% ± % bone demonstrated BIC at 12 weeks Coating A: 59% ± 20% Coating B: 59% ± 17% % Coating C: 930 ± 330 N Coating D: 1250 ± 90 N

2 and 12 weeks

Histomorphometry

µCT
Histomorphometry
N/A

Screw/thread
uncoated PEEK and Ti

smooth
unmodified PEEK

Screw/thread
uncoated PEEK

µCT
Histomorphometry
N/A

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

Zhao et al., 2016 Rat femur 8 weeks Plasma immersion ion implantation (PIII) with H2O (H2OPIII) or ammonia (NH2PIII) Significantly more bone volume on modified PEEK after 1 and 2 weeks when compared to uncoated PEEK. After 1 week, the BV of H2OPIII was 90% and NH2PIII 59% more than control. This trend was increased until the 2nd week, then maintained till the end of the 8th week PEEK: 36.5% H2OPIII: 46.4% NH2PIII: 48.5%

µCT
Histomorphometry
N/A

Zhao 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 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

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 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)
<table>
<thead>
<tr>
<th>Study</th>
<th>Model/duration</th>
<th>Type of modification</th>
<th>Finding/outcome</th>
<th>BIC</th>
<th>Evaluation method</th>
<th>Mechanical test</th>
<th>Implant design/comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouyang et al., 2016</td>
<td>Rat femur (Staphylococcus aureus) 8 weeks</td>
<td>PEEK sulphonation by sulphuric acid followed by hydrothermal treatment (25 and 120 °C) for removal of acid residuals (SPW25 and SPW120)</td>
<td>Smaller sulphur contents of SPW120 showed good antibacterial ability with accentuated bone formation</td>
<td>SPW120 showed direct bone formation and high BIC value in both histological and µCT evaluation</td>
<td>µCT</td>
<td>Histology</td>
<td>Smooth unmodified PEEK</td>
</tr>
<tr>
<td>Ma et al., 2016</td>
<td>Rabbits cranial defect 4 and 8 weeks</td>
<td>Biocomposite formation of n-CS/PEEK and n-HA/PEEK using compound and injection moulding</td>
<td>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</td>
<td>µCT 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</td>
<td>µCT</td>
<td>Histology, SEM</td>
<td>Smooth unmodified PEEK</td>
</tr>
<tr>
<td>Johansson et al., 2017</td>
<td>Rabbit tibia and femur 20 weeks</td>
<td>Nano-thick and size HA spin coating (HA/PEEK)</td>
<td>µCT showed no statistically significant difference between groups. Both groups showed intimate contact between PEEK and bone, as measured histologically</td>
<td>High BIC and BA values were found without a statistically significant difference with uncoated PEEK</td>
<td>µCT</td>
<td>Histomorphometry, Torque removal test</td>
<td>Screw/thread uncoated PEEK</td>
</tr>
<tr>
<td>Chen et al., 2017</td>
<td>Rat calvaria (Porphyromonas gingivalis) 8 weeks</td>
<td>Fluorinated PEEK by plasma immersion ion implantation (PIII) followed by hydrofluoric acid treatment (A-F/PEEK)</td>
<td>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</td>
<td>A-F/PEEK showed significantly larger bone biomarkers percentage when compared to unmodified PEEK</td>
<td>µCT</td>
<td>Histomorphometry, Bone labelling</td>
<td>Smooth uncoated PEEK</td>
</tr>
<tr>
<td>Study</td>
<td>Model/duration</td>
<td>Type of modification</td>
<td>Finding/outcome</td>
<td>BIC</td>
<td>Evaluation method</td>
<td>Mechanical test</td>
<td>Implant design/ comparator</td>
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<tr>
<td>Yang et al., 2017</td>
<td>Dog mandible (periimplantitis model) 8 weeks</td>
<td>n-HA PEEK composite coating for SLA implant</td>
<td>Untied groups showed less bone resorption than tied groups. Implant-bone interface in the united groups showed new bone formed directly on the implant surface</td>
<td>SLA-tied group showed lower BIC values than the n-HA-PEEK/SLA-tied group. n-HA-PEEK/SLA united group demonstrated significantly higher MAR. BIC and shear strength values than both tied groups. BIC in SLA united, n-HA-PEEK/SLA united, SLA tied and n-HA-PEEK/SLA tied was 76.98%, 78.82%, 58.35% and 67.98%, respectively</td>
<td>Histology</td>
<td>Bone labelling</td>
<td>Pull-out</td>
</tr>
<tr>
<td>Ahn et al., 2018</td>
<td>Rat tibia 8 weeks</td>
<td>PPP and PEEK smooth and porous implant designs</td>
<td>More bone formation revealed on PPP than PEEK</td>
<td>Porous PPP showed significantly more bone formation: 40% increase of bone volume as compared to smooth PPP and PEEK</td>
<td>μCT</td>
<td>Histology</td>
<td>Finite element</td>
</tr>
<tr>
<td>Yan et al., 2018</td>
<td>Rabbit femoral condyle 4, 8 and 12 weeks</td>
<td>Graphene modification of CRF PEEK (G-CRF-PEEK) surface</td>
<td>G-CRF-PEEK showed significantly higher BV/TV and TbTh values than CRF-PEEK at 4 and 8 weeks only</td>
<td>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)</td>
<td>μCT</td>
<td>Histology</td>
<td>Bone labelling</td>
</tr>
<tr>
<td>Hassan et al., 2018</td>
<td>Rabbit tibia 2 and 6 weeks</td>
<td>Nitrogen plasma treatment for PEEK (N₂PEEK)</td>
<td>New BA for N₂PEEK was significantly larger than for PEEK and Ti implants at 2 weeks. After 6 weeks, the N₂PEEK showed significantly higher value when compared to PEEK. At both time points, Ti implants showed significantly higher values than PEEK</td>
<td>N/A</td>
<td>Histology</td>
<td>Histomorphometry</td>
<td>Torque removal test</td>
</tr>
</tbody>
</table>
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.
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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation</th>
<th>Baseline characteristics</th>
<th>Allocation concealment</th>
<th>Random housing</th>
<th>Blinding of personnel</th>
<th>Random outcome assessment</th>
<th>Blinding of outcomes assessment</th>
<th>Incomplete outcomes data</th>
<th>Selective reporting</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakahara et al., 2012</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
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<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
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<td>Webster et al., 2012</td>
<td>Yes</td>
<td>?</td>
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<td>Poulsso et al., 2013</td>
<td>No</td>
<td>?</td>
<td>No</td>
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<td>No</td>
<td>?</td>
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<td>Yes</td>
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<td>Wang et al., 2014</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Lu et al., 2015</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Lee et al., 2015</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Guillot et al., 2016</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Yes</td>
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<td>Johansson et al., 2016</td>
<td>Yes</td>
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<tr>
<td>Ouyang et al., 2016</td>
<td>No</td>
<td>?</td>
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<td>?</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Ma et al., 2016</td>
<td>?</td>
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<td>Johansson et al., 2017</td>
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<tr>
<td>Yang et al., 2017</td>
<td>Yes</td>
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<td>Hassan et al., 2017</td>
<td>No</td>
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<td>Yes</td>
<td>Yes</td>
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</table>
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-TiO₂) or rutile phase (R-TiO₂) titanium could achieve better osseointegration. Both TiO₂ phases resulted in good bone formation on the implant surface. Importantly, R-TiO₂ showed significantly more BIC in histological assessment in addition to higher shear strength in mechanical tests. Based on these results, authors suggested that R-TiO₂ 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.](image-url)
Table 3. Summary of methods used for PEEK modification.

<table>
<thead>
<tr>
<th>Surface treatment</th>
<th>Coating</th>
<th>Bio composite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical:</td>
<td>• PEEK sulphonation</td>
<td>• CRF/PEEK</td>
</tr>
<tr>
<td>Physical:</td>
<td>• Nitrogen plasma (N2/PEEK)</td>
<td>• N-HA-CRF biocomposite</td>
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<tr>
<td></td>
<td>• Oxygen plasma (O2/PEEK)</td>
<td>+ oxygen plasma ± TiO2</td>
</tr>
<tr>
<td></td>
<td>• Plasma immersion ion implantation (PIII) with H2O2 (H2O2/PIII) or</td>
<td>blasting (PEEK/n-HA/CRF)</td>
</tr>
<tr>
<td></td>
<td>ammonia (NH3/PIII)</td>
<td>• n-HA/CRF-PEEK composite ± plasma</td>
</tr>
<tr>
<td></td>
<td>• ANAB</td>
<td>• n-FHA/PEEK</td>
</tr>
<tr>
<td></td>
<td>• Porous design</td>
<td>• n-CS/PEEK</td>
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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$_2$O$_3$ 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, binding 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.

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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.

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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.

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