# Surface modification of polyetheretherketone for boosted osseointegration: A review

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#### ABSTRACT

The field of orthopaedic implants has experienced rapid growth in recent decades, evolving from a few obscure examples to become one of the most vibrant domains within regenerative medicine. Polyetheretherketone (PEEK) stands out as a formidable competitor in this field due to its exceptional biocompatibility and appropriate mechanical strength. However, the clinical application of PEEK is limited by its inherent biological inertness. Therefore, numerous studies have focused on overcoming the bio-inert issue of PEEK using surface activation techniques. It is necessary to delve into the intricate effects of these modifications and their corresponding methods. In this review, we provide a comprehensive summary of contemporary research on surface modification for enhancing osseointegration of PEEK implants, categorising them into four parts based on their modification methods and techniques used: (1) physical treatment, (2) wet chemical methods, (3) combination of physical and chemical treatments, and (4) bioactive coating. Finally, we outline the challenges and unmet needs that must be addressed by future designs of PEEK surfaces. Overall, altering the surface morphology and/or surface group of PEEK to obtain a rough, porous, hydrophilic, and bioactive surface, or incorporating bioactive agents/coatings with bone-forming abilities onto the surface of PEEK has shown great potential for promoting osseointegration, which can serve as a solid foundation for subsequent clinical translation.

#### **Keywords**:

Coating; Orthopaedic implants; Osseointegration; PEEK; Surface modification

#### **1. Introduction**

Bone, as a critical component of the human body, possesses both stiffness and toughness due to its hierarchical organisation of organic matrix and inorganic minerals.1-3 With its exceptional mechanical properties, bone is capable of providing sufficient load-bearing ability for locomotion and protecting delicate internal organs.<sup>4-6</sup> However, fracture has become a common disease recently due to high energy traumas such as car accidents, sports injuries and industrial injuries, etc.7 In Europe, it is estimated that there will be an annual rise in fractures by 28% from 2010 to 2025, while age-related fractures in the United States are expected to increase from 2.1 million in 2005 to over 3 million in 2025.8,9 General speaking, small bone defects can regain their original structure and mechanical strength perfectly without leaving fibrotic scars.6 However, when the size of a bone defect caused by trauma, developmental

deformity, tumor resection, infection, etc. exceeds the critical threshold known as "criticalsize defect", self-healing becomes challenging and additional clinical intervention is often required.<sup>6</sup> The concept of critical-size defect was proposed by Schmitz and Hollinge<sup>10</sup> in 1986, and in adult patients, a bone critical-size defect is typically characterised by circumferential loss exceeding 50% or a length greater than 2 cm.<sup>11</sup>

Autologous and allogeneic bone grafts are frequently used to repair large bone defects.<sup>9,12</sup> Yet, they often suffer from the disadvantages of the limited supply of donor bone, blood disease transmission, immune rejection, and high costs.<sup>6</sup> Therefore, with recent advances in materials science, numerous biomaterials with designable and controllable properties have been applied to orthopaedic implants to overcome these problems, such as metals, ceramics, polymers and their composites.<sup>2,13-35</sup> However, each of these materials has certain limitations: (1)

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metallic materials may cause stress shielding and undesired release of metal ions; (2) bioceramics are susceptible to fracture owing to their inherent brittleness; and (3) polymers such as poly(L-lactide) and polytetrafluoroethylene lack sufficient strength to meet the mechanical requirements of orthopaedic implants.<sup>35,36</sup>

Polyetheretherketone (PEEK) composed of rigid benzene rings and ether and ketone bonds is a semi-crystalline specialty polymer. PEEK possesses numerous advantages, including suitable mechanical strength, outstanding biocompatibility, good resistance to wear and fatigue, and satisfactory radiation transmittance.<sup>36,37</sup> In particular, the elastic modulus of PEEK closely resembles that of human cortical bone, thus effectively mitigating the "stress shielding effect".<sup>37</sup> Consequently, back in the 1990s, PEEK received approval from the U.S. Food and Drug Administration for use as an orthopaedic implant,<sup>38</sup> and has been successfully utilised in spinal fusion devices, skull reconstruction and dental implants.37 The medical PEEK market reached approximately \$176.6 million in 2017 and is anticipated to grow to \$335.8 million by 2025, representing a growth of 90%.37 However, the lack of active groups in the main chain of PEEK makes it considerable biological inertia, which leads to poor osseointegration with host bone and limits its clinical applications to a great extent.<sup>37</sup>

In general, the strategies to improve the osseointegration ability of PEEK can be categorised into blending modification and surface modification.<sup>37,39</sup> Blending modification refers to a modification method of adding varying amounts of powders, particles, or fibres into the material matrix to obtain a performance-enhanced composite material.<sup>37</sup> This is a commonly used approach to improve the properties of PEEK, including its osseointegration ability. Different from blending modification, surface modification directly activates a material surface through physical or chemical means, thereby boosting its bioactivity without compromising its bulk properties. Numerous studies have shown that the construction of structures on PEEK surfaces that mimic the extracellular matrix of bone tissue, including chemical composition and topological geometry, can promote the osseointegration between its inert surface and natural bone tissue while stimulating the selfregeneration of the damaged bone tissue.<sup>36,40</sup>

In recent years, some reviews have mentioned the surface modification of PEEK, but this topic constitutes only a portion of their content, and the purposes of their modifications are not only to improve the osteogenic effect, but also to improve mechanical properties and other aspects.<sup>39-43</sup> Another recent review has highlighted biomolecule modification strategies on PEEK and its composites for osteogenesis and antibacterial properties.<sup>44</sup> Given the importance of surface modification and its potential for clinical translation, this review concentrates on the strategies to enhance the surface bioactivity of PEEK and their contributions to osseointegration. It is organised into

four parts: (1) physical treatment, (2) wet chemical methods, (3) combination of physical and chemical treatments and (4) bioactive coating. Each part is described thoroughly according to the fabrication methods (**Figure 1**), while we introduce the techniques and possible mechanisms behind each modification method and discuss their impacts on osseointegration. The advantages and disadvantages of common surface modification methods are listed in **Table 1**.<sup>45-62</sup> Finally, we highlight the unmet needs and future trends in the development of activated PEEK surfaces for better bone-tissue integration.

#### 2. Retrieval strategy

We searched Web of Science (https://webofscience.clarivate. cn/) with keywords as "(PEEK OR polyetheretherketone) AND (bone OR osteoge\*)". The research areas are "Materials Science", "Engineering", "Orthopedics", "Polymer Science", "Chemistry" and "Cell Biology", etc.

#### 3. Physical treatment

Physical treatment can quickly change the properties of material surface, such as roughness, wettability, and surface energy, and can even introduce different reactive groups to boost its biological activity. Meanwhile, these approaches are easy to be combined with following reaction steps to further expand the applications. However, one main drawback of physical treatment is a need for expensive equipment. At present, various physical treatment methods have been employed to physically modify PEEK, and this section highlights some commonly used methods. **Figure 2** presents a schematic diagram of three main physical modification methods.

#### 3.1. Sandblasting

Sandblasting, also known as abrasive blasting, is the operation of propelling abrasive materials or fine particles onto a surface at high speeds to clean, smooth, or roughen the surface. Given that increasing surface roughness can promote various biological responses such as cell adhesion, proliferation and differentiation,<sup>63,64</sup> this method has been used to improve the surface roughness of PEEK. For instance, Ishikawa's group<sup>65</sup> sandblasted PEEK surface with alumina particles to obtain a roughened surface. Scanning electron microscopy observation showed that the surface morphology of the sandblasted PEEK was significantly roughened, and the roughness of the PEEK surface increased from 0.06  $\mu m$  before treatment to 2.26 µm after sandblasting. In vitro experiments revealed that the surface of sandblasted PEEK remarkably improved the adhesion, proliferation, and bone-like nodule formation of rat bone mesenchymal stem cells (BMSCs) compared with untreated PEEK surface. Moreover, in vivo results showed that the sandblasted PEEK exhibited a higher pull-out force compared with untreated PEEK after implanting them into the rat femur bone marrow cavities for 2 or 4 weeks, indicating that the sandblasted PEEK has a greater osseointegration

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**Figure 1.** Typical strategies of surface modification for boosting the osseointegration of PEEK. Created with Adobe Illustrator 2020. Abbreviations: CaP: Calcium phosphate; PDA: Polydopamine; PEEK: Polyetheretherketone; PIII: Plasma immersion ion implantation.

Table 1.	The advantages and	disadvantages o	f different surface	modification	techniques
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Modification methods	Advantages	Disadvantages
Sandblasting	Increased surface roughness, low-cost, simple and rapid operation <sup>45</sup>	Contamination from the abrasive, difficulty to form nanoscale topography, poor reproducibility <sup>45,46</sup>
Plasma treatment	Increased surface hydrophilicity and roughness, introduction of functional groups, exclusion of the need for solvents, good scalability, uniformity, and repeatability <sup>47-49</sup>	Ageing effect: Partial or full reversibility of enhanced surface wettability <sup>47</sup>
PIII	No line-of-sight limitations, introduction of bioactive substances with strong adhesion, good uniformity and repeatability <sup>50</sup>	Heat generated during the process may cause the deformation of PEEK surface <sup>50</sup>
Sulfonation	Creation of surface porous structure, simple and rapid operation, low cost, applicable to complex shapes, introduction of sulfonyl groups, certain antibacterial activity <sup>51-53</sup>	Residual sulfonic acid is harmful to cells and tissues <sup>53</sup>
Surface polymerisation	Modification of surface chemistry, wettability, and roughness, introduction of various functional groups <sup>54</sup>	Not allowing for precise control of the architecture of the synthesised polymer <sup>55</sup>
CaP-like coatings	Similar to natural bone, good osteoinductivity <sup>56</sup>	Weak bonding strength between the coatings and the substrates $^{\rm 57}$
Graphene & GO coatings	Enhanced osteogenic differentiation of human MSCs, antibacterial properties <sup>58-60</sup>	Safety as biomaterials and coatings is still under investigation <sup>60</sup>
PDA-mediated bioactive coatings	Facilely loading a variety of bioactive substances, applicable to complex shapes, strong coating adhesion <sup>61</sup>	'Background adhesion' can decrease the cell viability and migration when PDA coating is $exposed^{62}$

Abbreviations: CaP: calcium phosphate; GO: graphene oxide; MSCs: mesenchymal stem cells; PDA: polydopamine; PIII: plasma immersion ion implantation.

ability. However, previous studies have indicated that the presence of aluminium (Al) ions inhibited the expression of the osteoblastic phenotype *in vitro*, and adversely affected on tissue reactions *in vivo*.<sup>45</sup> Therefore, the possible residue of alumina particles on the surface of PEEK should be concerned. Utilising a more biocompatible substance, such as calcium phosphate (CaP) particles, for sandblasting<sup>66</sup> may represent a better option.

#### 3.2. Plasma treatment

Plasma, often regarded as the fourth state of matter in addition to solid, liquid, and gas, is a fully or partially ionised gas generated by various charge carriers such as ions, electrons, and free radicals.<sup>67</sup> The reactive species generated by this method have higher energies than normal chemical bonds, enabling them to induce the breaking and reorganisation of chemical bonds on the polymer surface.<sup>39</sup> Consequently, this treatment process leads to alterations in both microscopic morphology and chemical composition.<sup>48,68</sup> For example, Liu et al.<sup>48</sup> treated PEEK surface with argon (Ar), nitrogen (N<sub>2</sub>), and Ar-N<sub>2</sub> plasma, respectively. The results showed that compared with the other two treatments, N<sub>2</sub> plasma treatment had the most obvious enhancement effect on osteogenic activity of mouse osteoblast precursor cells (MC3T3-E1 cells) due to the maximum roughness, strongest hydrophilicity and the introduction of nitrogen-containing functional groups, all of which have been proved to favour the osteogenic expression of osteoblasts.<sup>36,69</sup> Similarly, oxygen (O<sub>2</sub>) and hydrogen-oxygen (H<sub>2</sub>-O<sub>2</sub>) plasma



**Figure 2.** Schematic representation of three typical physical treatments: sandblasting, plasma treatment and PIII. Created with Microsoft PowerPoint 16. Abbreviations: PEEK: Polyetheretherketone; PIII: Plasma immersion ion implantation.

treatments were also conducted onto PEEK surface, which resulted in an improvement of cell adhesion.<sup>49</sup> Although various charge carriers are used, the essence of these plasma treatments is still to introduce different chemical groups on PEEK surface and alter its hydrophilicity and roughness. Obviously, these changes facilitate bone regeneration and integration.

#### 3.3. Ion implantation

Plasma immersion ion implantation (PIII) is a technique for surface modification. In PIII, the sample is surrounded via a high-density plasma and pulse-biased to a high negative potential with respect to the cavity wall, and subsequently ions produced in the plasma shroud are expedited through the sheath formed around the specimen and implanted into the target surface.70 The efficient transfer of ions from plasma to target surface makes PIII highly suited for highdose implantation of low-energy ions. Many metal elements have been proved to have excellent osteogenic effects.42,71 For example, elements such as calcium (Ca), magnesium (Mg), strontium (Sr), and zinc (Zn) play critical roles in bone immunomodulation; copper (Cu), Mg, and Zn are essential for neuromodulation; Mg, Sr, and Zn are pivotal in promoting angiogenesis, while Ca, lithium (Li), Mg, tantalum (Ta), and Sr are instrumental for bone metabolism and regeneration.<sup>71</sup> Therefore, PIII treatment provides an effective way to introduce and bind metal ions stably onto the surface of PEEK, thereby improving the osseointegration/bone remodelling ability of PEEK implants. In this field, Liu's group has done many excellent studies, and they introduced various metal ions such as Ti,<sup>72</sup> Zn,<sup>73</sup> Ca,<sup>74</sup> Ta,<sup>50</sup> Zr,<sup>75</sup> through PIII on the PEEK surface, resulting in varying degrees of improvement in the osteointegration ability of PEEK.

#### 3.4. Other methods

Surface topography of materials also plays a critical role in determining cell behaviour.<sup>76-86</sup> For instance, when cultured on substrates with varying morphologies, cells usually exhibit different spreading shapes, and there is a large amount of evidence suggesting that cell shape affects cell growth, migration, proliferation and differentiation.<sup>87-97</sup>

In bone repair, it is well known that the porous structure of implants has been shown to possess enhanced osteogenic capacity, but the bulk porosity generated by the blending method often leads to a decline in their mechanical properties.98 In contrast, surface porosity can provide a balance between improving bone integration and maintaining mechanical load bearing. To this end, Evans et al.98 pressed sodium chloride (NaCl) crystals with the size of approximately 250 µm onto the PEEK surface under high temperature and pressure, and then leached NaCl particles with water. The porous surface obtained could improve bone-implant fixation through enhanced mechanical interlocking, so the modified PEEK showed boosted osseointegration in vivo. Similarly, Boschetto et al.<sup>99</sup> introduced NaCl and  $\beta$ -silicon nitride ( $\beta$ -Si<sub>2</sub>N<sub>4</sub>) particles onto the surface of PEEK by hot pressing. Then, NaCl grains were removed by leaching in water, resulting in a porous PEEK surface embedded with  $\beta$ -Si<sub>2</sub>N<sub>4</sub> particles, which improved the osteogenesis and bacteriostasis of PEEK.

Femtosecond laser irradiation can create customised micronanostructures and patterns on the surface of various materials to facilitate cell adhesion and osteogenic differentiation.<sup>100,101</sup> This preparation method has the advantages of simplicity, rapidity, accuracy, reproducibility and low oxidation.<sup>102</sup> For instance, Xie et al.<sup>103</sup> fabricated a micro-nanotopography on PEEK surface using femtosecond laser, which significantly elevated the roughness, hydrophilicity and protein adsorption capacity of PEEK surface, thereby promoting the osteogenesisrelated gene expression of MC3T3-E1 cells. Additionally, Ji et al.<sup>104</sup> hydroxylated the surface of femtosecond laser-treated PEEK to further stimulate the osseointegration of PEEK.

In a recent study, Zhang et al.<sup>105</sup> used a hot die formation technique to construct patterned nanorod arrays with different diameters on the surface of PEEK (**Figure 3A**). Such approach could obtain evenly distributed nanorod arrays on the PEEK surface. *In vitro* studies demonstrated that PEEK embedded with 200-nm nanorod arrays (PEEK 200) exhibited the strongest osteogenic differentiation-inducing ability (**Figure 3B**). Furthermore, both PEEK and PEEK 200 were implanted into the distal femora of Sprague-Dawley rats. Four weeks later, micro-computed tomography observation showed that the extent of new bone formation in the PEEK 200 group was significantly better than that in the PEEK group (**Figure 3C**). Finally, haematoxylin and eosin and Ladewig staining validated



**Figure 3.** (A) Schematic illustration of the hot die formation technique to establish nanorod arrays with different diameters on PEEK surface. PEEK 100, PEEK 200, and PEEK 300 represent PEEK samples obtained from AAO templates with pore sizes of 100, 200 and 300 nm, respectively. (B) Osteoblast-specific gene analysis on day 14. Data are expressed as mean  $\pm$  SD. \**P* < 0.05, \*\**P* < 0.01, *vs*. PEEK plate; #*P* < 0.05, ##*P* < 0.01, *vs*. PEEK 100;  $\blacktriangle P < 0.05$ ,  $\bigstar P < 0.01$ , *vs*. PEEK 200. (C) 3D images of micro-CT scan. Scale bars: 0.5 mm. (D) H&E and Ladewig staining sections. The red arrows represent PEEK implants and the green arrows represent the new bone. Scale bars: 1 mm (upper), 0.5 mm (middle), 100 µm (lower). Reprinted from Zhang et al.<sup>105</sup> Copyright 2021 Wiley-VCH GmbH. Abbreviations: AAO: Anodic aluminium oxide template; ALP: Alkaline phosphatase; H&E: Haematoxylin and eosin; OCN: Osteocalcin; OPN: Osteopontin; PEEK: Polyetheretherketone; RUNX2: Runtrelated transcription factor 2; TCPs: Tissue culture plates.

that more new bone (pink in haematoxylin and eosin staining and blue in Ladewig staining) was detected around PEEK 200 (**Figure 3D**), indicating satisfactory osseointegration effects resulting from nanomorphological modification of PEEK.

#### 4. Wet chemical methods

Despite the outstanding chemical stability exhibited by PEEK, several chemical treatment approaches have been exploited for its surface decoration. These methods, collectively known as "wet chemical methods", involve immersing PEEK material into a reaction solution. Therein, surface sulfonation is the most popular wet chemical method. Additionally, some other wet chemical methods, such as surface polymerisation, are mentioned as well.

#### 4.1. Sulfonation

As early as 2001, Huang et al.<sup>106</sup> discovered that the benzene rings on PEEK can be electrophilically substituted with concentrated sulfuric acid to introduce sulfonic acid groups on its main chain (**Figure 4A**). At the same time, by controlling the sulfonation time, a porous structure less than 10  $\mu$ m can be created on PEEK surface (**Figure 4B**).

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The discovery of sulfonation is a considerable milestone in boosting the biological activity of PEEK. Next, Zhao et al.<sup>52</sup> found that the porous structure obtained by sulfonation could enhance the osseointegration of PEEK and bone-PEEK bonding strength in vivo, and preliminarily investigated the effects of residual sulfuric acid on cytotoxicity and osteogenesis using two post-treatment methods. Thereafter, they collaborated with Liu's group<sup>51</sup> to explore the effect of hydrothermal treatment temperature after sulfonation on the residual sulfate content and the corresponding cytotoxicity. It was found that hydrothermal treatment at 120°C for 4 hours could reduce the content of residual sulfuric acid to a very low extent, resulting in the sulfonated PEEK (SPEEK) exhibiting the strongest osteogenic activity both in vitro and in vivo. Furthermore, Ma et al.<sup>107</sup> compared different sulfonation time and post-treatment methods to evaluate their effects on the cvtocompatibility of MC3T3-E1 cells. The results indicated that prolonged sulfonation time tended to destroy and dissolve the porous structure formed on the PEEK surface and introduced more cytotoxic sulfur acid, which reduced the survival rate of MC3T3-E1 cells. Conversely, an approximately 5 minutes of treatment achieved the highest cell survival rate on the surface



PEEK

SPEEK

**Figure 4.** (A) Sulfonation reaction of PEEK. (B) SEM images of untreated PEEK (B1) and SPEEK (B2). Scale bars: 10 μm, 2 μm (enlarged images). Unpublished data. Abbreviations: PEEK: Polyetherethereketone; SEM: Scanning electron microscopy; SPEEK: Sulfonated PEEK.

of PEEK. Additionally, it was revealed that different posttreatment methods such as acetone washing, hydrothermal treatment and sodium hydroxide (NaOH) solution immersion did not differ significantly in the removal effectiveness of residual sulfuric acid.

Subsequently, with the development of research, several approaches have been reported to optimise the sulfonation process, such as the introduction of nitric acid on the basis of sulfuric acid to obtain hierarchical micro-nanostructures on PEEK surface,<sup>108</sup> and the treatment with NaOH solution after sulfonation to further improve its hydrophilicity.<sup>109</sup> Recently, Wan et al.<sup>110</sup> performed a sulfonation reaction on the PEEK surface using sulfur trioxide (SO<sub>3</sub>) gas, which displayed better controllability than concentrated sulfuric acid. Similarly, sulfate groups and porous structure were formed, both of which improved the osseointegration ability of PEEK implants.

#### 4.2. Surface polymerisation

Surface polymerisation is a novel surface modification method. One typical way is to generate free radicals on the main chain of PEEK and then to initiate the polymerisation of olefin monomers containing bioactive groups such as sulfonic acid and phosphoric acid, thereby introducing bioactive components onto PEEK surface. For instance, Ma et al.<sup>111</sup> grafted poly(sodium p-styrene sulfonate) onto the surface of PEEK by ultraviolet (UV) induced polymerisation to enhance its osteogenic activity (Figure 5). In vitro results demonstrated that osteo-differentiation of MC3T3-E1 cells were enhanced after modification and these enhancement effects became more obvious with the increase of grafting amount. In another attempt, Zheng et al.54 incorporated phosphate groups onto PEEK surface through the UV-initiated graft polymerisation of vinylphosphonic acid. In vivo evaluations indicated that the surface-phosphorylated PEEK exhibited improved boneimplant contact. In addition, it was also confirmed that the grafting time could modulate the content of phosphate groups on the PEEK surface, which further affected its osseointegration to a certain extent.<sup>112</sup>

Interestingly, suitable surface polymerisation can also produce specific surface topographies. For instance, polyacrylic acid chains were first grafted onto PEEK surface by UV irradiation. Then, ethylenediamine was added to promote the crosslinking of polyacrylic acid chains.<sup>113</sup> As a result, the modified PEEK surface not only exhibited significantly improved hydrophilicity, but also formed a micrometer-scale porous structure. Such modification further activated the focal adhesion kinase (FAK) pathway and Rho family GTPases, thereby improving cell adhesion and proliferation.

Moreover, in addition to free radicals, surface polymerisation of PEEK can also be carried out by introducing double bonds. For instance, Wang et al.<sup>114</sup> used sodium borohydride to reduce the carbonyl groups on the SPEEK surface to form hydroxyl groups. Next, the resulting samples were reacted with KH570, a silane coupling agent, to introduce C=C bonds. Afterward, a polyacrylic coating was grafted onto the surface and then amidised by ethylenediamine to form an aminated polymer surface. Finally, the samples were treated with excess of sodium hypochlorite to obtain N-Cl groups with antimicrobial activity. After implantation, the N-Cl functionalised surface efficiently prevented microbial infection. As antimicrobial oxidative chlorine atoms continued to be consumed at the bone defect site, the N-Cl groups were gradually turned to pro-osteogenic N-H groups at the later stage. Obviously, this strategy provides dynamic compatible bioactivities for PEEK implants at different stages of osseointegration after implantation in vivo.

#### 4.3. Other methods

Some other functional groups have also been introduced to the surface of PEEK through various chemical reactions.<sup>108,115,116</sup> For instance, Zheng et al.<sup>115</sup> modified -COOH, -OH and -PO<sub>4</sub>H<sub>2</sub> functional groups on the PEEK surface with the aid of silanisation treatment to enhance its bioactivity. Ding et al.<sup>108</sup> fabricated a hierarchical micro-nanoporous structure on the PEEK surface by adjusting the ratio of nitric acid to concentrated sulfuric acid. Subsequently, positively charged NH<sub>2</sub> groups were introduced onto the surface of PEEK by

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the Schiff base reaction between the keto carbonyl groups and ethylenediamine. The results showed that such double modification could endow PEEK with antimicrobial and osteogenic activities. In another attempt, Kassick et al.<sup>116</sup> obtained covalently modified hydrophilic PEEK surfaces with improved cell attachment and osseointegration by using the keto carbonyl groups of PEEK to react the same way with different oxyamine and hydrazine nucleophiles bearing polar end groups (Figure 6A, and B). In vitro cell experiments showed that upon addition of bone morphogenetic protein-2, the expression of alkaline phosphatase (ALP) and deposition of mineralised matrix in all the modified PEEK groups surpassed those in the unmodified PEEK group (Figure 6C). This indicates that this facile covalent modification method has potential to significantly improve the bone integration of PEEK.

## 5. Combination of physical and chemical treatments

The combination of physical and chemical treatments can amplify their respective advantages, so as to achieve better modification effects. For example, Wang et al.<sup>53</sup> used sulfonation combined with Ar plasma treatment to obtain a micro/nanotopographic PEEK surface with specific functional groups. Cellular experiments showed that this combination treatment significantly ameliorated the initial adhesion, proliferation and osteogenic differentiation of human osteoblast-like cells (MG-63) on the PEEK surface. In addition, the sulfonation process can soften the surface of PEEK. Taking advantage of this trait, Chen et al.<sup>117</sup> facilely fabricated a hierarchical topological structure on the surface of PEEK through sulfonation combined with "cold pressing" treatment mediated by NaCl porogenic agent (**Figure** 7). Subsequent



**Figure 5.** Schematic diagram of the UV-initiated surface grafting polymerisation and *in vitro* evaluation of pNaSS-grafted PEEK. Reprinted from Ma et al.<sup>111</sup> Copyright 2020 Wiley Periodicals, Inc.

Abbreviations: pNaSS: Poly(sodium p-styrene sulfonate); PEEK: Polyetheretherketone; UV: Ultraviolet.



**Figure 6.** (A) Covalent modification of PEEK surface with oxyamine and hydrazine nucleophiles. (B) Schematic diagram of the covalently modified PEEK surface with improved attachment and osteogenic expression of cells. (C) ALP levels of mouse myoblast cell line with or without BMP2 treatment and mineralisation levels of MC3T3-E1 cells with or without BMP2 treatment on various PEEK surfaces. Reprinted from Kassick et al.<sup>116</sup> Copyright 2018 American Chemical Society.

Abbreviations: ALP: Alkaline phosphatase; BMP2: Bone morphogenetic protein-2; Girard's T: Polymer 3c; ONH<sub>3</sub>: Polymer 3a; P15: Polymer 3d; PEEK: Polyetheretherketone; TC: Tissue culture polystyrene.

experiments demonstrated that the superficial porous structure contained 100–200  $\mu$ m macropores introduced by porogenic agent and 0.5–10  $\mu$ m micropores generated by sulfonation, which promoted new bone formation and achieved better bone integration with the surrounding host bone compared with pristine PEEK.

Similar to plasma treatment, PIII can also disrupt the molecular chains on PEEK surface and further generate free radicals to activate its surface. With the aid of PIII, researchers have introduced functional groups<sup>118-120</sup> and bioactive agents<sup>121</sup> on the PEEK surface while creating roughened and regular morphology.<sup>118,122</sup>

With the continuous refinement of the sulfonation treatment process, more and more studies have focused on the secondary modification of PEEK after sulfonation to further improve the osseointegration ability of PEEK.<sup>117,123-127</sup> For instance, Yuan et al.<sup>127</sup> added various concentrations of mouse beta-defensin-14 to the SPEEK surface and then immobilised it through lyophilisation. *In vitro* experiments showed that SPEEK incorporating mouse beta-defensin-14 had potent antibacterial activity against both *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa*, and promoted proliferation and osteogenic differentiation of BMSCs. The antibacterial activity and osseointegration potential of mouse beta-defensin-14-modified SPEEK were further confirmed by infected and uninfected rat femur models.

Diabetes-related bone defects have become one of the greatest challenges in bone repair due to the detrimental effects of chronic hyperglycaemia on osseointegration of implants.<sup>128</sup> To address this issue, Wang et al.<sup>129</sup> developed a Zn and Sr co-doped SPEEK implant (Zn&Sr-SPEEK) (**Figure 8A**). Hydrothermal treatment is an efficient method to introduce active substances.<sup>130,131</sup> Here, zinc oxide (ZnO) and strontium hydroxide (Sr(OH)<sub>2</sub>) nanoparticles were grown firmly onto the SPEEK surface through the electrostatic interaction of

the negatively charged groups (-SO<sub>2</sub>) of SPEEK with Zn and Sr ions during the hydrothermal process. This is then confirmed via Scanning electron microscopy observation (Figure 8B). In vitro biocompatibility experiments performed in a microenvironment simulating sustained hyperglycaemia demonstrated a significant enhancement in cell proliferation attributed to the sustained release of doped Zn and Sr ions from the Zn&Sr-SPEEK surface (Figure 8C). ALP and Alizarin Red S staining further confirmed that the *in vitro* osteogenic capacity of Zn&Sr-SPEEK was substantially improved (Figure 8D). Meanwhile, mitochondrial dynamics of MC3T3-E1 osteoblasts cultivated in high glucose medium containing different PEEK sample extracts were also evaluated. Mitotracker red staining results showed that the treatment of Zn&Sr-SPEEK improved the mitochondrial morphology and network structure, forming rod-like, elongated mitochondria and continuous mitochondrial network (Figure 8E). Besides, Zn&Sr-SPEEK implants effectively suppressed the overexpression of dynaminrelated protein 1 (Drp1) gene while reducing the levels of cellular reactive oxygen species, both of which contributed to the regulation of mitochondrial dynamics and functions in a hyperglycaemic micromilieu environment. Ultimately, the femoral/tibia bone defect model of diabetic rats revealed that co-modification with Zn and Sr could significantly promote the in vivo osseointegration of PEEK implants (Figure 8F).

#### 5.1. Bioactive coating

Another way to improve the bone integration of PEEK is to construct coatings on PEEK surface. Common methods for coating construction include chemical covalent bonding, physical adsorption, or the use of an adhesive medium. The modification methods discussed in the previous subsections only introduce bioactive agents to a portion of the PEEK surface, that is, the "new substance" added is isolated and discontinuous. In contrast, surface coating is to obtain one or more successive layers of "new substance" on the PEEK



**Figure** 7. Schematic illustration of the fabrication of a hierarchical porous structure on PEEK surface to enhance osseointegration. Reprinted from Chen et al.<sup>117</sup> Abbreviations: BSP: bone sialoprotein;  $H_2SO_4$ : sulfuric acid;  $O_2$ : oxygen; OCN: osteocalcin; OPN: osteopontin; PEEK: polyetheretherketone; SD: Sprague-Dawley.



**Figure 8.** (A) Schematic illustration of the fabrication of Zn and Sr co-decorated PEEK implants. (B) SEM images of different samples. (C) Viability of MC3T3-E1 cells cultured on different substrates for 1, 3, 5, and 7 days. (D1) Photographs of different functionalised PEEK samples. (D2) Photographs of ALP and Alizarin Red S staining of MC3T3-E1 cells on various substrates at indicated time points. Scale bars: 2 mm and 1 mm. (E1) Fluorescence images of Mitotracker Red staining. Scale bars: 10  $\mu$ m (upper), 2  $\mu$ m (lower). (E2) Relative expression of *Drp1* gene analysed at 24 hours by qRT-PCR. (E3) Mitochondrial ROS expression confirmed by fluorescent images. (F) Schematic diagram of the push-out experiment and the corresponding maximum push-out force. \**P* < 0.05, *vs.* PEEK; #*P* < 0.05, *vs.* SPEEK; +*P* < 0.05, *vs.* Zn-SPEEK; &*P* < 0.05, *vs.* Sr-SPEEK. Reprinted from Wang et al.<sup>129</sup> Abbreviations: ALP: alkaline phosphatase; Drp1: dynamin-related protein 1; mROS: mitochondrial reactive oxygen species; PEEK: polyetheretherketone; qRT-PCR: quantitative real-time polymerase chain reaction; SEM: scanning electron microscopy; SPEEK: sulfonated PEEK; Sr: strontium; Zn: zinc.

surface, thereby forming a new interface in contact with bone tissue. Therefore, the ability of these materials to bind to bone or promote bone growth is their selection criterion. In addition, these coatings can also impact the surface chemistry, morphology, and wettability of PEEK. It should be noted that the strong adhesion between the coating and the substrate is

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the key to the coating construction. Once the occurrence of coating shedding, the resulting particle debris may induce inflammation of the surrounding tissue, even causing bone resorption and implant failure.<sup>39</sup>

#### 5.2. CaP-like coatings

Multitudinous studies have confirmed that CaP has an excellent osteogenesis ability.<sup>132-141</sup> Hydroxyapatite (HAp), dicalcium phosphate dihydrate and beta tricalcium phosphate are three common forms of CaP.<sup>142</sup> Inspired by this, Almasi et al.<sup>143</sup> employed friction stir processing to cover HAp and NaCl particles onto the PEEK surface. Then, the sample was immersed in deionised water to leach out NaCl crystals while retaining HAp particles, thus obtaining a porous morphology. *In vitro* results showed that the introduction of HAp particles and porous structure contributed to improving cell adhesion, proliferation and differentiation compared with bare PEEK.

In addition to directly fastening CaP particles onto a material surface, CaP coatings can also be obtained by immersing the activated material in a simulated body fluid for a period of time.<sup>138,144,145</sup> To improve the binding force between the substrate and the coating, the fibre reinforced PEEK was first subjected to sulfonation and plasma treatment, followed by immersion in simulated body fluid solution at pH 8.4 and 25°C and being maintained at 70°C for 24 hours.<sup>146</sup> Scanning electron microscopy observation manifested that such treatment deposited fine amorphous CaP particles in the pores of PEEK and formed a CaP coating with high adhesion strength. After that, the coating-modified sample was implanted into a rabbit tibia model to test its osseointegration.<sup>147</sup> Histological observation and imaging analysis showed that the incorporation of amorphous CaP coating significantly enhanced the bone-implant bonding and promoted the formation of new bone.

It has been the grail to researchers to incorporate a variety of bioactive agents on the implant surface to improve its osseointegration and address other bone repair related issues such as bacterial infection and angiogenesis. In pursuit of this goal, Xue et al.<sup>148</sup> developed a dicalcium phosphate dihydrate coating containing gentamicin sulfate antibiotic on the PEEK surface (PEEK-DCPD-GS) using a layer-by-layer deposition method. In vitro antibacterial experiments demonstrated that PEEK-DCPD-GS had superior and sustained antibacterial activity. Meanwhile, the ability of MG-63 cells that are derived from human osteoblasts seeded on PEEK-DCPD-GS to secrete ALP was obviously enhanced compared with bare PEEK. In vivo evaluations employing a S. aureus infected rat femur defect model validated that PEEK-DCPD-GS could effectively control the occurrence of infection while promoting the formation of new bone. In another study, to orchestrate osteogenesis and angiogenesis during bone regeneration, Dong et al.<sup>56</sup> fabricated a multifunctional coating composed of HAp nanoflowers and nickel hydroxide nanoparticles on the SPEEK surface (SPEEK-Ni-HAp) through a two-step hydrothermal treatment (Figure 9). In vitro results showed that Ni and Ca ions could be sustainably released from SPEEK-Ni-HAp for over 7 days, and the introduction of Ni ions and HAp significantly enhanced the osteogenicity of SPEEK-Ni-HAp. Meanwhile, the loading and rational release of Ni ions fostered the migration, tube formation and angiogenic gene expression of human umbilical vein endothelial cells, indicating the good angiogenesis of SPEEK-Ni-HAp. Finally, in vivo experiments showed that the osseointegration ability of the Ni element and HAp nanoflower dual-modified PEEK was greatly boosted compared with SPEEK.

#### 5.3. Graphene & graphene oxide coatings

Graphene, a two-dimensional material, has received unprecedented attention over the last decade due to its large surface area, high mechanical strength, low mass density, and



**Figure 9.** Schematic illustrations of the preparation steps and performance evaluations of SPEEK-Ni-HAp implant. Reprinted from Dong et al.<sup>56</sup> Copyright 2020 American Chemical Society.

Abbreviations: EDTA: ethylenediaminetetraacetate; HAp: hydroxyapatite; SPEEK: sulfonated polyetheretherketone; VEGF: vascular endothelial growth factor.

good thermal and electrical conductivity.<sup>149,150</sup> A large number of studies have demonstrated that graphene can promote osteogenic differentiation of mesenchymal stem cells.<sup>150,151</sup> For instance, Yan et al.<sup>150</sup> transferred graphene onto the surface of carbon fibre-reinforced PEEK. The rabbit extraarticular graft-to-bone healing model confirmed that the graphene modification significantly promoted the osseointegration of carbon fibre-reinforced PEEK implants.

As one of the most popular graphene derivatives, graphene oxide (GO) is a monatomic nanosheet with dense honeycombstructure composed of sp<sup>2</sup>-hybridised carbon atoms, and contains abundant oxygen-containing functional groups (hydroxyl, carboxyl, etc.), which make it easy to achieve good bonding with other substances.<sup>152,153</sup> Meanwhile, some studies have revealed that GO can enhance osteogenic differentiation of mesenchymal stem cells and MC3T3-E1 cells<sup>154,155</sup> and has antiadhesion and antibiofilm activities.<sup>155,156</sup> The contribution of GO to osteogenic differentiation of stem cells may stem from the regulation of mitochondrial dynamics within stem cells,157 the enhancement of body fluid mineralisation capacity,<sup>158</sup> and the ability to remodel a biomimetic regenerative electrophysiological microenvironment at the defect sites due to its inherent electrical conductivity.<sup>159</sup> Inspired by these studies, Ouyang et al.<sup>160</sup> introduced a GO coating onto the SPEEK surface via a simple dip-coating method. The GO coating exhibited good durability due to the potent  $\pi$ - $\pi$  stacking interactions between SPEEK and GO. Antibacterial experiments demonstrated that the modification of GO improved the antibacterial performance against Escherichia coli (E. coli) compared with SPEEK and PEEK. Moreover, GO-modified SPEEK had higher attachment, proliferation, bone-like nodule formation and osteogenic differentiation-related gene expression of MG-63 cells than SPEEK and unmodified PEEK. It should be noted that these studies have demonstrated the efficacy of graphene/GO coatings in animal studies, but their mechanisms of action are not vet clear, which poses a considerable barrier to their clinical translation. Therefore, it is urgent to conduct more in-depth discussion and research on their mechanisms.

#### 5.4. Polydopamine-mediated bioactive coatings

In the past decade, polydopamine (PDA) coatings inspired by marine mussels have attracted considerable attention due to their facile preparation, excellent adhesion and good biocompatibility.62,161-164 Numerous studies have focused on the construction of PDA coatings on material surfaces and subsequent utilisation of their interactions such as hydrogen bonding,  $\pi$ - $\pi$  stacking, coordination bonding, and chemical reactions such as Michael addition and Schiff base reactions stemmed from its benzene ring, amino and hydroxyl groups to immobilise a variety of bioactive agents, thereby enhancing the osteogenesis ability of materials.<sup>156,165-168</sup> As its application in PEEK, for instance, Shi et al.<sup>169</sup> fabricated a coating of bionic natural bone composed of collagen and CaP on the PDA-modified PEEK surface through layer-by-layer method combined with in situ mineralisation. The results showed that the introduction of biomimetic interface promoted the osteogenic differentiation of MC3T3-E1 cells in vitro, which made the modified PEEK have a stronger osteogenesis effect in vivo.

In addition to promoting osteogenesis, PDA coatings also allow the simultaneous introduction of bioactive agents with antibacterial, anti-inflammatory, and angiogenic properties onto the PEEK surface to further enhance the osseointegration capability of PEEK implants.<sup>61,170-175</sup> For example, Meng et al.<sup>170</sup> immobilised the antimicrobial peptide KR-12 on the surface of PEEK with the assistance of PDA coating, which significantly boosted the antimicrobial and osteogenic activities of PEEK both in vitro and in vivo. Similarly, Xiao et al.<sup>171</sup> constructed a bimetallic-organic framework coating composed of Mg<sup>2+</sup>, Zn<sup>2+</sup>, and 2,5-dihydroxyterephthalic acid (Zn-Mg-MOF74) on the PEEK surface (PEEK-74) by using the strong adhesion force and metal ion chelating ability of PDA interlayer, and then loaded the surface of Zn-Mg-MOF74 coating with dexamethasone (DEX) (PEEK-DEX) (Figure 10A). In vitro osteogenic results showed that the ALP expression and matrix mineralisation formation of BMSCs in the PEEK-DEX group were better than those in the other three groups thanks to the release of Zn and Mg ions and DEX. Blood vessel formation experiments revealed that compared with the other two samples, PEEK-74 and PEEK-DEX exhibited more intersections in the new vascular network (Figure 10B), indicating their good angiogenic ability. This was attributed to the release of Mg ions. Figure 10C presents the antibacterial activity of various PEEK samples against E. coli and S. aureus. Similar to blood vessel formation, PEEK-74 and PEEK-DEX showed excellent antibacterial performance. This feature was due to the alkaline microenvironment formed by the degradation of their coatings as well as the release of Zn and Mg ions and 2,5-dihydroxyterephthalic acid. Finally, the rat femoral implant model confirmed that a multifunctional coating (DEX@Zn-Mg-MOF74) on the surface of PEEK-DEX with antibacterial, angiogenic, and osteogenic functions promoted osteointegration in vivo (Figure 10D).

Interestingly, the roughened and porous SPEEK surface plus the presence of sulfonic acid groups contributes to forming a firmer PDA coating with PEEK substrate. Based on this strategy, using PDA as the interlayer, various bioactive agents/coatings have been introduced onto the SPEEK surface to enhance its osseointegration ability, such as Arg-Gly-Asp tripeptide,<sup>176</sup> gentamicin sulfate,<sup>177</sup> strontium carbonate (SrCO<sub>3</sub>)/gentamicin-silk protein,<sup>178</sup> moxifloxacin hydrochloride/osteogenic growth peptide,179 strontium/ adiponectin,130 insulin-like growth factor-1 (IGF-1) and BMP-2,180 icariin,181 Cu-Sr bilayer bioactive glass nanoparticles,182 glucose oxidase,<sup>183</sup> GO/DEX-loaded liposome,<sup>184</sup> copper ferrite (CuFe<sub>2</sub>O<sub>4</sub>)/GO,<sup>185</sup> etc. It should be noted that the sulfonation and subsequent PDA layer (or the PDA layer only) provide almost exclusively the anchoring function, while the osteogenic, angiogenic, and antimicrobial functions of the coatings are generated by the introduced bioactive agents. Therefore, the osseointegration efficiency of modified PEEK is mainly attributed to the attachment-release behaviour of the bioactive agents and their bioactivity in a variety of different situations (e.g., osteoporosis, hyperglycaemia, etc.).

Additionally, with the aid of PDA, Deng-Yang's research group incorporated some biological active agents onto the GO-modified SPEEK surface to further enhance its osteogenesis and antibacterial



**Figure 10.** (A) Schematic diagram of the fabrication of multifunctional DEX@Zn-Mg-MOF74 coating on PEEK surface. (B) Representative images of HUVEC angiogenesis assay and *in vivo* CAM assay on various PEEK surfaces. Scale bars: 400  $\mu$ m (left), 0.5 cm (right). (C) Antibacterial activity of different PEEK samples. (D) Micro-CT observation and reconstructed 3D models. The red arrows mark new bone formation. Scale bars: 2.5 mm. Reprinted from Xiao et al.<sup>171</sup> Copyright 2021 American Chemical Society.

Abbreviations: CAM: chicken chorioallantoic membrane; CT: computed tomography; DEX: dexamethasone; DEX@Zn-Mg-MOF74: zincmagnesium based metal organic framework loaded with dexamethasone; DHTA: 2,5-dihydroxyterephthalic acid; *E.coli: Escherichia coli*; HUVECs: human umbilical vein endothelial cells; MOF: metal-organic frameworks; PDA: polydopamine; PEEK: polyetheretherketone; PEEK-74: PEEK coated with zinc-magnesium based metal organic framework; PEEK-PDA: PEEK coated with PDA; *S.aureus: Staphylococcus aureus*.

activities.<sup>186,187</sup> For instance, they coated the GO-modified SPEEK surface with a PDA coating and then introduced a bone-forming peptide, resulting in a multifunctional coating (**Figure 11A**).<sup>186</sup> *In vitro* evaluations showed that the combination of bone-forming peptide and GO increased the viability, ALP expression and calcium nodule formation of MC3T3-E1 cells, thereby achieving the best osteogenesis-promoting effect (**Figure 11B**). *In vivo* experiments based on a rabbit femoral defect model demonstrated that the hybrid coating prominently boosted bone regeneration and osseointegration. Meanwhile, when exposure to 808 nm near-infrared light for 10 minutes, the hybrid coating showed excellent antibacterial activity against *S. aureus* and *E. coli* (**Figure 11C**). This was attributed to the synergetic photothermal/ photodynamic efficacy generated by GO nanosheets and PDA interlayer.

#### 5.5. Other bioactive coatings

Inspired from drug delivery systems, many studies began to focus on the construction of drug delivery coatings on the PEEK surface using microspheres, hydrogels, etc., to precisely control the release of loaded bioactive agents.<sup>188-194</sup> Hydrogels, in particular, are suitable as reservoirs for drug delivery due to their simple preparation, good biocompatibility and soft matter nature.<sup>195-207</sup> For example, Dong et al.<sup>194</sup> sulfonated long carbon fibre reinforced PEEK (CP) to obtain a porous CP implant (SCP), and then immersed it into a mixed solution of gelatin methacrylate/acrylamide (GelMA/AM). Under UV irradiation, free radicals were generated on the backbone of SCP, which initiated the polymerisation of GelMA and AM, resulting in the formation of a GelMA/AM gel coating (GC)



**Figure 11.** (A) Schematic diagram of the fabrication of GO/BFP-decorated SPEEK implant (SPEEK-GO-BFP). (B) *In vitro* evaluation of cell viability, ALP expression, and matrix mineralisation formation. (C) Photothermal properties and antibacterial activities of the hybrid coating with or without light. Data are expressed as mean  $\pm$  SD. \**P* < 0.05, \*\**P* < 0.01; &*P* < 0.05, &&*P* < 0.01, *vs*. other groups. Reprinted from Wang et al.<sup>186</sup> Copyright 2020 The Royal Society of Chemistry.

Abbreviations: ALP: alkaline phosphate; BFP: bone-forming peptide; *E.coli: Escherichia coli*; GO: graphene oxide; OD: optical density; PEEK: polyetheretherketone; *S.aureus: Staphylococcus aureus*; SPEEK: sulfonated PEEK; SPEEK-BFP: BFP-modified SPEEK; SPEEK-GO: GO-immobilised SPEEK.

on the SCP surface (SCP-GC). Ultimately, DEX was absorbed onto the surface of SCP-GC via hydrogen bonding to harvest DEX-loaded SCP-GC. As a result, a three dimensional network was formed on the GC-modified SCP surface. The components of hydrogel coating coupled with the sustained release of DEX significantly promoted ALP expression and bone-like apatite nodule formation of BMSCs. The rat cranial defect model showed that the DEX-loaded hydrogel coating promoted the formation of new bone around the implant, resulting in a stronger implant-bone interface.

#### 6. Limitations

This review focuses on the material design of PEEK surface modification and its contribution to the osteointegration of PEEK. However, due to the article's length and thematic perspective, this review has the following limitations: (1) In recent years, with the deepening of the understanding of bone repair, researchers have found that stem cells, immune cells and nerve cells, etc. have a strong correlation with bone regeneration. This review does not elaborate on the impact of PEEK surface modification on this aspect. (2) The biological effects of the physicochemical properties of modified PEEK surfaces on tissues and cells are not discussed in depth, and their relevant rules need to be further summarised. (3) The biological mechanisms by which the active substances introduced onto the PEEK surface contribute to pro-osteogenic effects are not much involved.

#### 7. Summary and prospect

This review summarises the main surface modification methods that have been used in recent years to improve the osseointegration of PEEK implants and categorised them into four parts based on the modification methods and techniques used, that is, (1) physical treatment, (2) wet chemical methods, (3) combination of physical

and chemical treatments, and (4) bioactive coating. All of these modification methods have altered the surface state of PEEK to a certain extent, i.e., increasing surface roughness, hydrophilicity, porosity, and/or introducing bioactive groups/agents/coatings, thereby boosting its osseointegration. Meanwhile, we have also demonstrated the powerful capability and numerous applications of sulfonation layer and/or PDA layer as an interlayer to bind bioactive agents/coatings.

Bone defect repair involves various cell types, including osteoblast cell lines, angiogenic cell lines, and immune cells, as well as the corresponding interactions of cells and cellbiomolecules/materials, making it a multi-stage and dynamic process. Tissue engineering is an advanced technique for tissue repair.<sup>208-229</sup> As a matter of fact, the aforementioned modification strategies of PEEK surface align with the prevailing modification strategies employed in bone tissue engineering scaffolds. The essence of tissue engineering scaffold is to design a material structure close to natural bone tissue and incorporate appropriate bioactive molecules to modulate the osteogenic and angiogenic/neurogenic microenvironments, thereby promoting bone regeneration and facilitating bone-implant bonding. Therefore, the key aspect of PEEK surface design lies in achieving a biomimetic interface and precise delivery of bioactive molecules/components. Particularly important is ensuring that the release behaviour of these bioactive molecules/ components matches the process of bone repair/regeneration.

Meanwhile, as regenerative medicine advances, there is an increasing demand for precision and personalised treatment among patients. This necessitates constructing customised PEEK implant surfaces tailored to individuals with different bone defect conditions based on accurate diagnoses. 3D-printed PEEK can be a potential development direction. Researchers have proposed some surface modification strategies for 3D-printed PEEK, including a sand casting-inspired technology to produce BG coatings,<sup>230</sup> a combined method of sulfonation and UV-induced grafting to introduce gel coatings,<sup>231</sup> and a PDA coating-mediated approach for the introduction of bioactive metal ions.<sup>232</sup> However, traditional line-of-sight surface modification techniques such as plasma treatment, sandblasting and sputtering are not suitable for the complex topography of 3D-printed PEEK.<sup>230</sup> Consequently, the surface modification of 3D-printed PEEK remains an area that needs to be explored in depth.

Additionally, standardising unmodified PEEK specimens, surface analysis methods and *in vivo* animal models will facilitate comparison across different studies on surface modifications. Finally, before these surface treatments can be implemented clinically, some practical issues such as stability during storage, resistance to sterilisation procedures, and wear resistance must be addressed to ensure that these modifications remain intact during preparation and implantation.

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#### Conflicts of interest statement

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent for publication

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