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Review

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Modification of polyetheretherketone (PEEK) physical features to improve osteointegration

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Abstract: Polyetheretherketone (PEEK) has been widely applied in orthopedics because of its excellent mechanical properties, radiolucency, and biocompatibility. However, the bioinertness and poor osteointegration of PEEK have greatly limited its further application. Growing evidence proves that physical factors of implants, including their architecture, surface morphology, stiffness, and mechanical stimulation, matter as much as the composition of their surface chemistry. This review focuses on the multiple strategies for the physical modification of PEEK implants through adjusting their architecture, surface morphology, and stiffness. Many research findings show that transforming the architecture and incorporating reinforcing fillers into PEEK can affect both its mechanical strength and cellular responses. Modified PEEK surfaces at the macro scale and micro/nano scale have positive effects on cell–substrate interactions. More investigations are necessary to reach consensus on the optimal design of PEEK implants and to explore the efficiency of various functional implant surfaces. Soft-tissue integration has been ignored, though evidence shows that physical modifications also improve the adhesion of soft tissue. In the future, ideal PEEK implants should have a desirable topological structure with better surface hydrophilicity and optimum surface chemistry.

Key words: Polyetheretherketone (PEEK); Surface topography; Architecture; Stiffness; Bone integration

1 Introduction

Millions of people suffer bone defects in response to trauma, tumors, or congenital malformations (Swetha et al., 2010). Such events have promoted the rapid development of bone substitute materials in attempts to restore damaged bone functions. Ideal bone grafting substitutes possess mechanical properties for load-bearing applications as well as osteoconductivity, osteoinductivity, and biocompatibility (Petite et al., 2000). Titanium (Ti) and its alloy currently are the first choice for orthopedics and dental implants because of their excellent biological and mechanical properties. However, they have some limitations, including an elastic modulus mismatch, stress shielding, toxic metal ion release, and medical imaging artifacts that interfere with observation of the post-operation healing phase (Kurtz and Devine, 2007; Mishra and Chowdhary, 2019).

Polyetheretherketone (PEEK) is a semi-crystalline, synthetic polymer that was approved by the US Food and Drug Administration in the late 1980s (Kurtz and Devine, 2007). Because of its excellent biocompatibility, fatigue resistance, mechanical properties, and radiolucency, PEEK has been widely applied in orthopedics, trauma treatments, spinal implants, and joint replacement (Kurtz and Devine, 2007; Mishra and Chowdhary, 2019). The elastic modulus of PEEK (3–4 GPa) is closer to that of cortical bone (18 GPa) than to that of titanium alloy (about 110 GPa). This comparatively close compatibility aids in the prevention of negative stress-shielding effects (di Maggio et al., 2017; Mishra and Chowdhary, 2019).

However, the bioinert nature of PEEK, together with poor bone conduction, has greatly limited its use in clinical trials and applications (Deng et al., 2015; Spece et al., 2020). Recently, efforts have focused on increasing the bioactivity of PEEK through two different strategies, namely, surface modification and bioactive

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particle incorporation into PEEK substrates (Almasi et al., 2016; Buck et al., 2020). Accumulating evidence proves that the physical factors of implants, including their architecture, surface morphology, stiffness, and mechanical stimulation, are as important to implant design as their chemical composition (Hao et al., 2017; Tian et al., 2019; Rangel et al., 2020). Although previous studies have proposed techniques to modify the physical properties of PEEK (Khoury et al., 2017; Han et al., 2019b; Wang L et al., 2019), there is still no consensus on the optimum design.

This paper provides a review of multiple strategies for the physical modification of PEEK implants through adjusting their architecture, surface morphology, and stiffness. The effects of these changes on the bioactivity and osteogenesis of PEEK are outlined and discussed. Finally, we provide an outline of the properties of materials to be further explored and discuss directions for future PEEK development.

2 Architecture of implants

The macrodesign of an implant is important for its stability, both during and after osteointegration. Implants need to be designed to minimize extreme negative stresses to the bone implant interface while also delivering optimal favorable stresses to the greatest extent (Abuhussein et al., 2010). An example of this is dental implants, in which the implant shape was transformed from hexagonal to conical, and now includes a thread pattern in the surface to achieve long term stability (le Guéhennec et al., 2007; Abuhussein et al., 2010).

At the macroscale, bone consists of external cortical bone and internal cancellous bone (trabecular bone) and has a highly interconnected and porous architecture (with pore size ranging from 20 to 400 μm) (Vallet-Regí and Ruiz-Hernández, 2011). Bone substitutes are designed to be structurally similar to this, including having a porous structure. Pore size is kept between 100 and 600 μm, as this range is necessary for cell penetration and vascularization, allowing for better material integration with surrounding tissue (Jarman-Smith et al., 2011; Vaezi and Yang, 2015). There are several techniques for manufacturing PEEK of a specific geometry or porous structure, including three-dimensional (3D) printing and porogen leaching. However, little consensus has been reached on the optimum pore size and pattern of scaffolds for PEEK manufacture.

2.1 3D printing

Additive manufacturing (AM), also known as 3D printing, is able to produce patient-specific implants (Attaran, 2017). The AM technologies most commonly used for PEEK manufacture are selective laser sintering (SLS) and fused deposition modelling (FDM) (Hoang et al., 2016). These technologies have the ability to produce a customized PEEK shape with variable surface roughness together with an intrinsic porous structure. Implants that are 3D-printed and customized have been used clinically for craniofacial reconstruction (Sharma et al., 2020).

Characteristics such as pore size and pore morphology have integral effects on the bioactivity and mechanics of implants. To determine the best pore size of PEEK scaffolds, Feng et al. (2020) designed PEEK implants with a settled porosity of 60%, but with pore sizes of 300, 450, and 600 μm. PEEK implants designed with macropores (450 and 600 μm) performed better than solid PEEK in terms of their cell-seeding efficiency, proliferation, microvascular perfusion ability, and new bone formation ability. Spece et al. (2020) reported that different constructs (e.g., rectilinear, gyroid, or diamond) with a similar pore size (600 μm) showed analogous cell activity. However, in terms of mechanical properties, the diamond construct had significantly greater yield strength than others. Roskies et al. (2016) managed to fabricate porous PEEK scaffolds by modifying the internal structure to form a trabecular network by making use of the SLS technique. The trabecular-like scaffold was able to sustain the viability of both adipose-derived mesenchymal stem cells (adMSCs) and bone marrow stromal cells (BMSCs), and also supported the osteodifferentiation of adMSCs. Overall, 3D printing of PEEK implants revealed limited biocompatibility when compared to 3D-printed porous Ti alloy (Tsai et al., 2021). PEEK scaffolds were found to have a higher range of motion and less bone volume within the graft window (McGilvray et al., 2018). Combining 3D printing with other modification technologies may solve this problem. For example, surface coating with calcium hydroxyapatite (HA) contributed to both enhanced mechanical strength and biological activity

in vivo (Oladapo et al., 2020). Greater cellular infiltration and biological integration of PEEK composites within surrounding tissue were found in porous PEEK/HA composites (Vaezi et al., 2016).

The average surface roughness of untreated 3D-printed PEEK was 22.28 μm, decreasing to 0.17–0.52 μm after polishing or sandblasting (Han et al., 2019b). Studies have shown that 3D-printed PEEK without polishing or sandblasting showed stronger osteointegration because of its roughness and unique printing structure, specifically the distinct peaks and valleys on its surface (Han et al., 2019a, 2019b). The highly roughened surfaces of untreated PEEK provide an enlarged available surface area. The manufacturing process results in cell accumulation in surface grooves, which might promote the establishment of cell–cell contacts and enhance cell viability (Berent and Johnson, 2020; Zhang et al., 2020).

2.2 Porogen leaching

In scaffold design, pore interconnectivity (permeability) is essential for cell behavior, vascular formation, and nutrient delivery, in addition to an optimum pore size (Yu D et al., 2020). Porous PEEK implants with pore diameters of 100–600 μm and high interconnected porosity (>65%) can be fabricated by way of porogen leaching. PEEK powder blended with space-holding filler materials, such as sodium chloride (NaCl), is considered molten or solvent, and can be cast to create a composite. This composite is then leached in a solution to remove the porogen (Hou et al., 2003; Siddiq and Kennedy, 2015; Yuan et al., 2018). In addition, the porous structure increases implant stability in vivo by encouraging new bone ingrowth, whereas dense samples have only small amounts of bone creeping growth on the surface edge (Hieda et al., 2017; Yuan et al., 2018). The study by Conrad and Roeder (2020) showed that an ellipsoidal porogen facilitated improved pore interconnectivity and permeability when compared to a cubic porogen. Additive material incorporated into porous structures of PEEK implants helps further improve the osteointegration of porous PEEK. Bioactive materials incorporated into PEEK substrates include nano-bioglass (Zhang et al., 2018), mesoporous diopside (Cai et al., 2017), biphasic bioceramics (Yu et al., 2018), nanoporous lithium-doped magnesium silicates (Wang L et al., 2019), and silicon nitrides (Boschetto et al., 2021).

As mentioned above, the advantage of PEEK is that its elastic modulus is similar to that of bone. Introduction of a macropore structure can impair the mechanical properties of PEEK, which limits its clinical application. Increased porosity (75%–90%) leads to a non-linear decrease in elastic modulus and strength yields for PEEK implants (Converse et al., 2009). The increased compressive yields on stress and stiffness for samples with 84% porosity were about 1 and 30 MPa, respectively (Siddiq and Kennedy, 2015). Researchers have previously tried to incorporate additive fillers, such as carbon nanotubes, carbon fibers, and HA whiskers, into wholly porous PEEK to enhance its mechanical properties (Converse et al., 2009; Uddin et al., 2019); however, efficacy has thus far been limited. Therefore, for clinical applications of porous PEEK, implantation sites should be carefully selected, paying attention to the matching of the materials and the mechanical properties of surrounding tissues. Better ways to manufacture porous PEEK so that its strength matches that of the surrounding bone structures still need to be developed. Optimizing the structural design of the material may also be an option (Cheng et al., 2020).

3 Modification of surface morphology

3.1 Macroscale surface modification

Overall, macroporous structures degrade the mechanical properties of PEEK. Some studies have proposed that limited macroscopic structural modification to the surface of the substrate can solve this problem (Zhou et al., 2010; Torstrick et al., 2016). Large-scale surface features can support bone ingrowth as well as increased mechanical interlocking, while retaining mechanical properties.

3.1.1 Melt extrusion technique

Torstrick et al. (2016) and Evans et al. (2015) developed a novel method to fabricate PEEK with porosity limited to that of the implant surface. NaCl crystals were pressed into PEEK under heat and high-pressure conditions. After cooling, the embedded NaCl crystals were resolved in water, and a porous surface layer was left without changing the chemical composition. Pore sizes can be reliably controlled by adjusting the diameter of the NaCl crystals (ranging

from 200 to 500 μm), and interconnectivity can reach 99.9%. Mechanical tests revealed that surface porous PEEK preserved over 70% of the strength and elastic modulus of solid PEEK, with the pore layer shear strength being significantly improved (Evans et al., 2015). Surface porous PEEK promotes the proliferation of osteoblasts at the early stage (48 h) and accelerates the differentiation and mineralization of osteoblasts. Different pore sizes showed no differences in the support of cell growth (Torstrick et al., 2016). However, cell numbers at later time points were lower than those of smooth PEEK surfaces. This result was in response to hypoxic conditions for cells residing within the deeper pores (as shown by increased vascular endothelial growth factor (VEGF) production) (Torstrick et al., 2016). Adjusting the thickness of the porous layer may solve this problem. Hypoxia may be reduced and nutrient diffusion improved by vascularization into the pore network when surface porous PEEK enters the body. However, more experiments are needed to evaluate the in vivo angiogenesis and osteointegtation of surface porous PEEK. Surface porosity improves implant stability by encouraging bone ingrowth within the pore layer to produce greater implant fixation and less fibrous encapsulation (Evans et al., 2015). At eight weeks after implantation into the proximal tibiae of rats, the force required to remove the implant was increased by 3.4-fold compared to that of implants with smooth interfaces (Torstrick et al., 2018). However, the study also showed lower bone-implant contact (BIC) at the bone-implant interface on surface porous PEEK than on plasma-sprayed Ti-coated PEEK, indicating insufficient bioactivity of surface porous PEEK (Torstrick et al., 2018). Future studies should consider incorporating other modifications to improve the osteogenesis of surface porous PEEK.

Based on their successful mechanical and biological performance in previous studies, spinal fusion PEEK implants incorporating a surface porous structure have been included in clinical applications (Torstrick et al., 2017). Positive short-term results have been achieved in some patients, but long-term follow-up is needed. Furthermore, interactions between PEEK scaffolds with the host bone still need to be investigated.

3.1.2 Laser ablation

Laser ablation has many advantages for producing polymers with microstructures. It is also a non-contact procedure with high controllability and reproducibility. Characterized by the application of heat to a small region while controlling depth (Duncan et al., 2002), the advantages of this technique are its fast operation, low cost, preservation of bulk properties, and possibility of processing various materials (Riveiro et al., 2012). Laser ablation of parallel microgooves can be found in a variety of polymers, including PEEK.

Surface pores with diameters ranging from 200 to 600 μm have been manufactured by laser treatment. An in vitro test of MC3T3-E1 showed more cell adhesion and proliferation on 400-μm macropores than on pores of other sizes (Huang et al., 2021). Cordero et al. (2013) produced parallel microgrooves, about 40 μm in width, separated by distances of 25, 50, 75, and 100 μm, with unchanged chemical compositions. However, the surface wettability was slightly improved; namely, the contact angles of irradiated areas were reduced by 5%. MC3T3-E1 osteoblasts grew by following the direction of the parallel grooves and were most pronounced using the 25-μm pattern. Gheisarifar et al. (2021) also reported that elongated human gingival fibroblasts (HGFs) with more pseudopods aligned on laser-grooved PEEK surfaces, but the precise channel size was not mentioned (Gheisarifar et al., 2021). Enhanced cell adhesion in micro-grooved surfaces may result from the increased contact areas, as well as the better integration of cell pseudopods and collagen microfibrils with the surface (Weiner et al., 2008). Riveiro et al. (2012) found that different laser irradiation wavelengths not only affect surface morphology, but also alter surface hydrophilicity. Results showed that ultraviolet (λ=355 nm) laser radiation enhances surface wettability most effectively, but has only a slight thermal effect on the surface structure.

Combinations of different surface modification techniques and laser texturing can further enhance cell behavior. Hierarchically patterned PEEK surfaces consist of both nanostructures and microstructures, with improved surface wettability successfully produced by combining plasma etching and pulsed laser ablation (Akkan et al., 2013; Zheng et al., 2015). Plasma treatment introduces surface carboxyl groups onto PEEK surfaces, whereas laser treatment constructs microgrooves 58 μm in width with 250 μm distance between them, over the PEEK surface. The highest initial cell adhesion for 4 h and later cell proliferation was found on dual-modified PEEK (Zheng et al.,

2015). A similar result was observed in HGFs (Gheisarifar et al., 2021).

3.2 Microscale and nanoscale surface modifications

Micron-sized topography and proper surface roughness have been shown to affect cell behavior and bone formation (Zhuang et al., 2021). Proper surface roughness facilitates absorption of extracellular matrix (ECM) proteins, which is necessary for initial cell adhesion. The extracellular domains of integrins then bind specifically to ECM peptide ligands, i.e., the tripeptide Arg-Gly-Asp (RGD). Following this, various cellular signal pathways are activated and nuclear deformation is induced, finally affecting gene expression, cell morphology, migration, proliferation, and differentiation (Kechagia et al., 2019). It is recognized that not only the scale of morphology, but also the degree of order (random, half-ordered, and ordered), type of morphology (e.g., ridges, steps, grooves, pillars, or pits), and symmetry regulate cell function (Biggs et al., 2010; Gui et al., 2018). There are various techniques for manufacturing PEEK with microscale surface morphology, for example, sandblasting, sulfonation, and plasma treatment. Different morphologies can be obtained by applying the different techniques. In this section, we discuss the effects of each method on the surface morphology and biological activity of the material.

3.2.1 Sandblasting

It is well known that roughened Ti, or Ti alloy prepared using a sandblast technique, gives enhanced osteoconductivity and implant osteointegration ability compared with machined surfaces (Grassi et al., 2006; Elias et al., 2008). Previous research focused on the effect of sandblasting PEEK surfaces, during which abrasive particles, such as aluminum oxide (Al_2O_3), titanium oxide (TiO_2), and silicon oxide (SiO_2), are usually used to roughen PEEK surfaces. The surface roughness depends mainly on the size of the abrasive particles. Deng et al. (2015) evaluated the impact of surface roughness on the cellular responses of osteoblast-like MG-63 cells and in vivo osteointegration. Treatment with different Al_2O_3 particle grit sizes increased PEEK surface roughness from (0.12±0.01) to (0.93±0.09) μm (low roughness), (1.96±0.21) μm (moderate roughness), and (2.95±0.35) μm (high roughness). The results revealed that PEEK with moderate surface roughness had the best cell attachment, proliferation, and osteogenic activity among all groups. In addition, the greatest percentage of BIC was found on the moderately roughened implant (Deng et al., 2015). Alumina particles induced a PEEK surface with medium roughness at about 2.3 μm, whereas the roughness of polished PEEK was only 0.06 μm (Sunarso et al., 2018). Micro-roughening significantly improves the proliferation and differentiation of BMSCs, as shown by cell counting kit-8 (CCK-8) and alkaline phosphatase (ALP) activity. Additionally, the pull-out force of roughened surface PEEK was about four times higher than that of polished surfaces, indicating that sandblasting promotes implant-bone integration (Sunarso et al., 2018). Some studies showed mild improvements in surface cell response on PEEK surfaces treated with sandblasting (Fukuda et al., 2018; Gültan et al., 2020).

The surface bio-performance of PEEK composites incorporating bioactive particles can greatly improve following sandblasting (Deng et al., 2015; Tang et al., 2017). For example, cell responses to nano-calcium silicate (n-CS)/PEEK composites, including cell attachment, cell spreading, proliferation, and osteogenic differentiation, were significantly promoted after sandblasting compared to untreated composites (Tang et al., 2017). Scanning electron microscope (SEM) confirmed that more bioactive materials were exposed on composite surfaces when treated with sandblasting (Deng et al., 2015). The same effect was observed in PEEK composite treated with abrasive paper. However, cell behaviors were not significantly improved on abraded surfaces (Cai et al., 2018; Mei et al., 2019). Therefore, we believe that sandblasting can improve the biocompatibility of PEEK by introducing surface roughness.

3.2.2 Sulfonation

PEEK is chemically inert because of its structure of aromatic molecular backbones with combinations of ketone and ether functional groups between aryl rings (Panayotov et al., 2016). However, by conducting sulfonation in concentrated sulfuric acid, 3D, porous, nanostructured networks, and SO_3H groups can be successfully introduced into PEEK surfaces (Zhao et al., 2013). Pore diameter ranges from 0.5 to 1.0 μm, and the thickness of the modified layer is about 100 μm. On sulfonated PEEK, osteoblast functions are all

ameliorated, including initial cell adhesion, cell viability, proliferation, differentiation, bone regeneration, and apatite formation (Zhao et al., 2013). However, the residual sulfur and low-pH environment have been reported to have adverse impacts on osteoblast cell behavior and new bone formation (Meng et al., 2004; Zhao et al., 2013). Appropriate post-treatment methods, such as hydrothermal treatment (Cheng et al., 2019), acetone washing (He et al., 2019), and NaOH rinsing (Wang WG et al., 2019), help remove excess sulfur. Recently, Ma et al. (2020) systematically compared different acid treatment time and post-treatment methods by examining cellular behavior and surface morphology. Immersion time was 0.5, 1, 3, 5, and 7 min, and the post-treatment methods included acetone rinsing, hydrothermal treatment, and NaOH immersion. Results showed that the optimal sulfonation time was 5 min, and different post-treatment methods had an equivalent effect in eliminating residual sulfuric acid and cell reaction.

Surface wettability affects the in vivo rate of osseointegration by regulating the absorption of macromolecules and adjusting cell interaction between substrates and the surrounding tissue (Han et al., 2019b). Studies have shown that sulfonation leads to only limited bioactivity improvement. This may be due to decreased hydrophilicity on sulfonate PEEK, which may reduce the beneficial effects of chemical structures and surface morphologies on cell reactions. However, previous studies have indicated an increase in hydrophilicity. Wang WG et al. (2019) found that NaOH immersion following short-time sulfonation (about 20 s) helped reduce the PEEK water contact angle from 78° to 37°. Another study found that a significant reduction in contact angle of sulfonated PEEK was produced after 24 h of NaOH treatment, without any change in surface morphology or chemical structure (Cheng et al., 2019). A further study by Miyazaki et al. (2017) reported that hydrophilicity increased for all substrates after sulfonation, followed by 24-h immersion in a 1 mol/L $CaCl_2$ solution. For PEEK treated with 80% (volume fraction) sulfuric acid for 3 h, the contact angle (92.7°±2.3°) showed a greater reduction (to 53.6°±5.3°) than hydrophilicity after sulfonation. Modified samples promoted better MSC growth and proliferation (Yuan et al., 2016). The combination of various surface treatment methods with sulfonation, such as plasma treatment, can also ameliorate the cell response by enhancing surface hydrophilicity (Yabutsuka et al., 2017; Wang et al., 2018).

3D porous surfaces manufactured with sulfonation are ideal for drug loading. Researchers have successfully immobilized functional biomolecules and drugs to the 3D porous PEEK surface to improve bone conductivity. For example, cell proliferation and the expression of bone formation-related genes were promoted after phosphorylated gelatin loaded with bone morphogenetic protein 2 was coated on sulfonated PEEK. Combined with a bioactive coating, the behavior of MC3T3-E1 was further improved compared with sulfonated PEEK (Wu et al., 2018). However, these methods have limitations. Firstly, it is difficult to control the release rate and local concentration of active molecules in an in vivo environment (Guillot et al., 2016). In addition, non-covalently bound proteins do not adhere well to the substrate and are likely to detach from the surface.

3.2.3 Plasma treatment

Plasma, also known as the fourth state of matter, is defined as an ionized gas with an equal density of positive and negative charges (Fu et al., 2021). Plasma striking the material surface breaks the covalent bond and disrupts the polymerization chain, leading to changes in the surface chemical composition, topography, and hydrophilicity (Wang et al., 2014; Zhao et al., 2016). This effect has been used to amplify the bonding strength between dental prostheses of PEEK and veneering composites and enhance the biocompatibility of PEEK implants (Waser-Althaus et al., 2014).

Compared to untreated surfaces, plasma-treated PEEK exhibits higher hydrophilicity (Fu et al., 2021). The effect of plasma treatment depends on the process gases. Carboxyl and hydroxyl groups are introduced after oxygen plasma treatment, whereas more carbon single bond hydroxyl groups are introduced after hydrogen plasma treatment (Fu et al., 2021). Surfaces with more nitrogen-containing functional groups are manufactured after ammonia or N_2 plasma treatment (Briem et al., 2005). Water plasma treatment forms more OH groups on surfaces (Wang et al., 2014). Wang et al. (2014) demonstrated that the osteogenesis of MC3T3-E1 and rat BMSCs (rBMSCs) were enhanced by the ravined nanostructure (arithmetic average roughness (Ra)=15.3 nm). The expression of osteogenic differentiation-related genes was upregulated

after 2 d, indicating that protrusions and a ripple-like surface with an average roughness of less than 15.7 nm also effectively promote osteointegration (Zhao et al., 2016). Similarly, Waser-Althaus et al. (2014) found that pillar-like structures in the range of 10 nm show better osteogenic differentiation than does PEEK with greater roughness. However, several studies have shown that higher roughness is more suitable for supporting cell behavior. Gan et al. (2016) produced PEEK with nanostructured surfaces of different roughness (Ra=436, 443, or 608 nm) by N_2-plasma immersion ion implantation (PIII). With the increase of surface roughness, cell proliferation, viability, and ALP activity were improved remarkably. MC3T3 osteoblasts showed the best osteogenic activity on PEEK-N_2/argon (Ar) cold plasma treatments with moderate roughness ((150.20± 5.23) nm), as indicated by ALP staining. In contrast, surface roughness of the material showed no obvious change after low-pressure plasma treatments, whereas cell adhesion on the surface of the material was still significantly improved (Fu et al., 2021). The inconsistency of the optimum roughness scale may be related to the variable chemical composition and surface morphology following different plasma treatments (Table 1).

3.2.4 Accelerated neutral atom beam

Accelerated neutral atom beam (ANAB) is a surface treatment technique, in which the PEEK surface is bombarded with atoms from of a neutral reactive species generated by a gas cluster ion beam (Kirkpatrick et al., 2013; Khoury et al., 2019). The technique has an extremely shallow penetration and causes dimples no deeper than 2–3 nm without changing the surface chemical composition (Awaja et al., 2012).

The roughness of ANAB-treated PEEK (Ra= (3.45±0.52) nm) is slightly lower that that of control samples (Ra=(4.63±0.78) nm) (Khoury et al., 2019). However, a nano-texture was manifested in ANAB-treated PEEK surfaces (ranging from 10 to 50 nm). This texture may substantially enhance surface hydrophilicity and thus promote the attachment, proliferation, and differentiation of osteoblasts and BMSCs (Khoury et al., 2013, 2017). The growth of human MSCs, skin fibroblasts, and human osteoblasts showed that both metabolic activity and proliferation were significantly increased on ANAB PEEK compared to an untreated control. Additionally, the increased levels of ALP of MSCs seeded on ANAB PEEK in the presence of osteogenic media indicated that ANAB treatment may improve osteointegration (Ajami et al., 2017). ANAB treatment also affects the behavior of dental pulp stem cells with pronounced genetic distinction, indicating earlier progression toward osteogenic differentiation (Khoury et al., 2019). In in vivo studies with ovine bone, an ANAB-treated sample showed evidence of bone ingrowth at both early and later stages. This resulted in a 3.09-fold improvement in BIC and a 2.07-fold increase in push-out strength, compared with untreated PEEK controls (Khoury et al., 2017). Taken together, ANAB processing has great potential to ameliorate the bioactivity and bone generation of PEEK surfaces by producing nano-textured surface profiles.

4 Modification of PEEK stiffness

Substrate stiffness plays a significant role in the regulation of cell behavior including differentiation, proliferation, migration, and apoptosis (Chaudhuri et al., 2020). For example, MSCs tend to differentiate into osteoblasts when the matrix rigidity matches that of the surrounding bone tissue (11–40 kPa), whereas they tend to differentiate into myoblasts on matrices that mimic striated muscle elasticity (Engler et al., 2006). Generally, a reconstruction material with elasticity matching that of the surrounding tissue is beneficial for integration (Ochsner, 2011). The elastic modulus of PEEK is far below that of Ti, which effectively avoids stress shielding. However, the elastic modulus of pure PEEK material (3–4 GPa) is lower than that of cortical bone (6–30 GPa) (Lee et al., 2012). Deficiencies in mechanical strength limit the application of PEEK as a bone substitute, especially when applied in a bearing zone. This will encourage the development of new techniques to modify mechanical strength (Qin et al., 2019; Gao et al., 2020).

Carbon materials, such as carbon nanotubes and carbon fiber, are often used as reinforcing fillers to prepare polymer composites. Compared with that of pure PEEK, the modulus of PEEK composites incorporating carbon fiber or carbon nanotubes is increased from 7.7 to 11.5 GPa, matching the modulus of human cortical bone (Hassan et al., 2018; Qin et al., 2019). However, results have been inconsistent concerning the cytotoxicity of carbon fiber-reinforced (CFR)-PEEK.

Table 1 Characteristics and biological properties of plasma-treated polyetheretherketone (PEEK)

Reference	Plasma type	Surface feature	Surface roughness Ra	Chemical composition	Cell type	Cell reaction
Fu et al., 2021	Hydrogen (H), oxygen (O), H/O plasma treatments	Not mentioned	H-PEEK: (0.42±0.07) μm; O-PEEK: (0.40±0.07) μm; H/O-PEEK: (0.43±0.06) μm Untreated PEEK: (0.41±0.07) μm	COOH and OH groups were introduced onto the surface	Human osteoblasts	Cell density: O-PEEK=H/O-PEEK>H-PEEK=untreated PEEK
Wang et al., 2014	Argon (Ar), Ar/water (A/W) plasma immersion ion implantation (PIII)	Ravined structure	Not mentioned	OH groups were introduced onto the surface	MC3T3-E1	Cell adhesion and spreading: A/W-PEEK>Ar-PEEK>untreated PEEK; ALP activity: A/W-PEEK>untreated PEEK>Ar-PEEK
Zhao et al., 2016	H_2O, NH_3 PIII	Surface protrusions and a ripple-like topography	Between 10.45 and 15.7 nm	H_2O PIII: C=O groups were introduced; NH_3 plasma: nitrogen-containing functional groups and C=O groups were introduced	MC3T3-E1 pre-osteoblasts	Cell adhesion and proliferation ↑, ALP activity ↑, osteogen-related gene expression ↑, mineralization tests ↑
Waser-Althaus et al., 2014	O/Ar, NH_3 plasma treatments	Pillar-like structures	In the range of 10, 25, and 50 nm	Oxygen plasma: O/C ratio ↑; Ammonia plasma: introduction of surface-amino groups	adMSCs	Adhesion, proliferation, and ALP activity ↑: 10-nm surface showed best results
Briem et al., 2005	NH_3/Ar plasma treatment	Not mentioned	Not mentioned	Nitrogen-containing functional groups (50% being amino groups)	Primary fibroblasts and osteoblasts	Primary fibroblasts: proliferation and adhesion ↑; Osteoblasts: ALP activity, collagen production, and mineralization ↑
Gan et al., 2016	N_2-PIII	Uniformly distributed granules	Ra=436, 443, or 608 nm	Nitrogen-containing functional groups were introduced	Human osteoblast-like MG63 cells	Cell attachment, proliferation viability, ALP activity: surface with Ra of 600 nm showed best results
Liu et al., 2021	Ar, N_2, Ar/N_2 cold plasma treatments	Scaly nano-protrusions appeared on the PEEK-Ar and PEEK-Ar/N_2 surfaces; dendritic nano-protrusions on the PEEK-N_2 surface	N_2-PEEK: (192.60±5.89) nm; Ar/N_2-PEEK: (150.20±5.23) nm; Ar-PEEK: (99.60±5.43) nm	Nitrogen-containing functional groups to the PEEK on all three surfaces	MC3T3-E1	Cell adhesion, cell viability, and ALP activity ↑: N_2-PEEK>Ar/N_2-PEEK>Ar-PEEK>untreated PEEK
Chen et al., 2017	Ar PIII (A), Ar PIII followed by immersion in HF solution (AF)	Nano-protrusion	Not mentioned	Fluorine was introduced	rBMSCs	Cell adhesion, cell proliferation and ALP activity ↑: AF-PEEK>A-PEEK>untreated PEEK
Awaja et al., 2012	CH_4+O_2 or CH_4 plasma treatment	Oxygen-rich nanofilms	Not mentioned	Oxygen, nitrogen, and C–O functional groups	MG63 cells	Cell adhesion and spreading ↑

adMSCs, adipose-derived mesenchymal stem cells; ALP, alkaline phosphatase; HF, hydrogen fluoride; Ra, arithmetic average roughness; rBMSCs, rat bone marrow stromal cells.

Han et al. (2019b) found no cytotoxicity on CFR-PEEK. Two other studies reported that the addition of carbon fiber showed mild toxicity, and that the cytotoxicity increased with increasing carbon fiber content (Qin et al., 2019), but was independent of fiber length (Li et al., 2019). Differences in CFR-PEEK manufacturing techniques may have contributed to the inconsistent results. Therefore, more investigation is required to identify the biocompatibility of CFR-PEEK. In addition, CFR-PEEK tends to exhibit higher bioactivity than does pure PEEK when applied to other surface modification techniques as additional carbon phases (Miyazaki et al., 2017; Qin et al., 2020). HA is also commonly used to fill PEEK composites. The elastic modulus of the composites increases, but the tensile strength decreases, as the HA content increases, which means that the composites have high stiffness, but are brittle (Converse et al., 2007; Ma and Guo, 2019). Owing to the excellent biocompatibility of HA and its chemical similarity to the inorganic constituents of natural bone, the biological functions (both in vitro and in vivo) of HA-PEEK are considerably improved (Li et al., 2012; Yu XZ et al., 2020). Other fillers, such as nano-TiO_2 (Wu et al., 2012), tantalum nanoparticles (Zhu et al., 2019), and silica fibers (Monich et al., 2017), can also improve mechanical properties while maintaining or improving the biological activity of the composite. Making alterations to the elastic modulus of PEEK may have only a small impact on bioactivity. This may be because the elasticity modulus of pure PEEK is already close to that of natural bone. Therefore, the improvement of composite biocompatibility depends more on filler bioactivity.

5 Soft tissue

Current research is centered on improving the bone-binding properties of PEEK while ignoring soft-tissue integration. Nevertheless, the long-term success of implants depends not only on stable osteointegration, but also on the uniform integration of substrate surfaces with surrounding soft tissues (Griffin et al., 2016; Wang YL et al., 2016). This is especially important in the maxillofacial region where implants are in contact with large areas of soft tissue. Significantly more multinucleated giant cells were found on PEEK surfaces than on Ti closure caps, indicating a stronger foreign body reaction on PEEK (Caballé-Serrano et al., 2019). Therefore, the soft tissue integration ability of PEEK still needs to be improved.

Studies have found that the surface morphology of PEEK may affect soft tissue adhesion. Gheisarifar et al. (2021) found more functionally oriented HGFs and enhanced cell adhesion presented on laser-grooved surfaces. The proliferation of HGF cells was improved by plasma treatment. Wang X et al. (2016) fabricated a unique multilevel TiO_2 nanostructure on CFR-PEEK using the Ti PIII technique. They found that the migration activity formation of focal adhesions along with the expression of ECM-related genes of HGFs was promoted because of the nanoscale surface. Microporous surfaces fabricated by acid-etching encourage human skin fibroblast adherence as well as the expression of soft tissue growth genes, whereas internal cross-linked structures with macropore diameters of 1.0–2.0 mm encourage ingrowth of soft tissues (Feng et al., 2019). PEEK with 1.5-mm porous specimens showed a better mechanical combination with soft tissues (Feng et al., 2019).

6 Conclusions

PEEK implants with multi-scale topography show considerable potential as a biomaterial for bone grafting applications. Various techniques have been explored to enhance their osteointegration by changing the PEEK structure and surface morphology (Fig. 1). However, unlike porous scaffolds, which are more common in bone-tissue engineering, PEEK is more like a prosthetic implant for bone defect reconstruction than a bone substitute. So, it is vital to preserve bulk properties to maintain the mechanical strength of PEEK in most application scenarios. Therefore, we believe that techniques which preserve the overall mechanical properties of PEEK are superior to others. Techniques like porogen leaching that introduce a wholly porous structure could decrease material elastic modulus and strength. Melt extrusion technique, laser ablation, and other techniques that limit topography alteration to the material surface have successfully promoted osteointegration while retaining mechanical properties. 3D printing is a more flexible method that generates implants with specially designed structures tailored

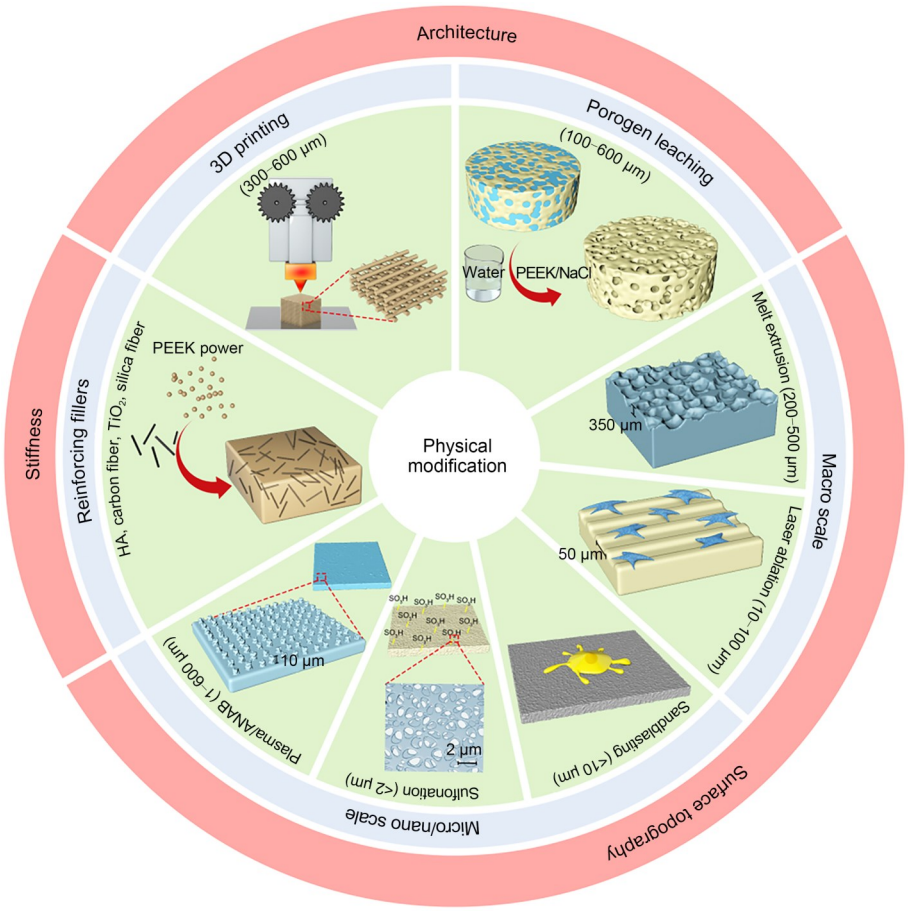

Fig. 1 Techniques for the physical modification of polyetheretherketone (PEEK) implants through adjusting its architecture, surface morphology, and stiffness. Three-dimensional (3D) printing and porogen leaching are common methods to manufacture PEEK of a specific geometry or porous structure. Techniques that change surface topography are categorized into two classes: macro-scale methods (including melt extrusion technique and laser ablation); micro/nano-scale methods (including sandblasting, sulfonation, plasma treatment, and accelerated neutral atom beam (ANAB)). To increase stiffness, PEEK composites that contain reinforcing fillers are fabricated. HA: hydroxyapatite.

to different clinical scenarios. With the development of computer-aided design (CAD) and topology optimization, clinical applications of 3D-printed PEEK will become more accepted and extensive in the coming decades.

PEEK implants with variable scales of porous structures each have their own advantages; however, none of the methods we mentioned has been able to fulfill all the requirements of bone substitutes. Therefore, a single change in physical structure may be of limited benefit. We should expand our focus to combine surface modifications, such as wettability and chemical composition. PEEK with optimized surface bioactivity might be obtained by combining a desirable topological structure with better surface hydrophilicity and chemical modification. Finally, the integration of implant surfaces with surrounding soft tissues should not be neglected.

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Author contributions

Dan YU was responsible for concept design, literature research, and manuscript writing. Xiaoyue LEI contributed to literature research, wrote and edited the manuscript. Huiyong ZHU was responsible for review and quality control of the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Dan YU, Xiaoyue LEI, and Huiyong ZHU declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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