

Bioactivity and Osseointegration of PEEK Are Inferior to Those of Titanium: A Systematic Review

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Polyetheretherketone (PEEK) has been suggested as an alternative to replace titanium as a dental implant material. However, PEEK's bioactivity and osseointegration are debatable. This review has systematically analyzed studies that have compared PEEK (or PEEK-based) implants with titanium implants so that its feasibility as a possible replacement for titanium can be determined. The focused question was: "Are the bioactivity and osseointegration of PEEK implants comparable to or better than titanium implants?" Using the key words "dental implant," "implant," "polyetheretherketone," "PEEK," and "titanium" in various combinations, the following databases were searched electronically: PubMed/MEDLINE, Embase, Google Scholar, ISI Web of Knowledge, and Cochrane Database. 5 in vitro and 4 animal studies were included in the review. In 4 out of 5 in vitro studies, titanium exhibited more cellular proliferation, angiogenesis, osteoblast maturation, and osteogenesis compared to PEEK; one in vitro study observed comparable outcomes regardless of the implant material. In all animal studies, uncoated and coated titanium exhibited a more osteogenic behavior than did uncoated PEEK, while comparable bone-implant contact was observed in HA-coated PEEK and coated titanium implants. Unmodified PEEK is less osseointegrative and bioactive than titanium. Furthermore, the majority of studies had multiple sources of bias; hence, in its unmodified form, PEEK is unsuitable to be used as dental implant. Significantly more research and long-term trials must focus on improving the bioactivity of PEEK before it can be used as dental implant. More comparative animal and clinical studies are warranted to ascertain the potential of PEEK as a viable alternative to titanium.

Key Words: polyetheretherketone, titanium, osseointegration, bioactivity

INTRODUCTION

An endosseous dental implant is a device surgically inserted into the jaw bone to support a prosthodontic or orthodontic appliance.¹ Titanium is the most commonly used dental implant material.² However, it has a number of drawbacks: First, being nonesthetic, it discolors the underlying gingival of thin biotype.³ Second, because the modulus of elasticity of titanium is higher than that of bone, titanium may cause bone resorption by shielding the alveolar bone from occlusal stresses that are needed to maintain bone volume—a phenomenon known as "stress shielding."⁴ Furthermore, there have been cases of titanium allergy in patients receiving dental implant.⁵ Therefore, alternatives to titanium are being studied. Zirconia (zirconium oxide), an esthetic ceramic material, is a possible replacement for titanium implants. However, since its modulus of elasticity is much higher than that of bone, it may lead to stress shielding.⁶

More recently, polymeric implant materials have been developed. Polyetheretherketone (PEEK) is a tooth-colored polymer, produced from the step-growth alkylation reaction of bisphenolates, and it has multiple applications in orthopedics.⁷ PEEK has been used as an implant material in spinal surgery, fracture fixation devices, joint replacement, and maxillofacial surgery.^{8–11} In dentistry, PEEK has been used in the construction of CAD/CAM-milled fixed and removable bridges¹² as well as removable dentures and crowns.¹³ Because of PEEK's superior esthetics and modulus of elasticity—close to that of the human bone—it has been proposed as a dental implant material as well.¹⁴ However, the potential of PEEK to replace titanium as dental implant material is still debatable. While some studies suggest that unmodified PEEK has osseointegrative properties similar to titanium,¹⁵ others suggest that it does not promote mature osteoblast differentiation as much as does titanium.¹⁶ Therefore, this review systematically analyzed studies that have compared PEEK or PEEK-based implants with titanium implants to determine its feasibility as a possible replacement for titanium.

MATERIALS AND METHODS

Focused question

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the following focused question was constructed according to the Participants

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Intervention Control Outcomes principle¹⁷: "Are the bioactivity and osseointegration of PEEK implants comparable to or better than titanium implants?"

Selection criteria

The following inclusion criteria were used: (1) studies on osseointegration and/or bioactivity of PEEK (modified or unmodified) and titanium implants, (2) human trials, (3) animal studies, (4) cell-culture (in vitro) studies, and (5) articles in English. The exclusion criteria were: (1) letters to the editor, (2) reviews, and (3) short communications.

Search methodology

Using the keywords "dental implant," "implant," "polyether-etherketone," "PEEK," and "titanium" in various combinations, the following databases were searched electronically: PubMed/MEDLINE, Embase, Google Scholar, ISI Web of Knowledge, and Cochrane Database. Two reviewers (S.N. and Z.K.) searched independently, according to the inclusion and exclusion criteria. A secondary search was conducted by going through the reference lists of articles obtained in the primary search. Any disagreements were settled by a third reviewer (M.S.Z).

RESULTS

Search results

As illustrated in the Figure, of the 25 articles obtained following the primary search, full texts of 11 articles were read. Two articles were excluded for not meeting the inclusion criteria. Hence, 9 articles (5 in vitro studies and 4 animal studies) were included in the review.^{15,16,18–20} The general characteristics and outcomes of the included in vitro and animal studies are summarized in Tables 1 and 2, respectively.

Main outcomes of selected studies

In 4 out of 5 in vitro studies, titanium exhibited stimulated more cellular proliferation, angiogenesis, osteoblast maturation, and osteogenesis compared to PEEK,^{16,18–20} and comparable outcomes were observed in one in vitro study regardless of the implant material.¹⁵ In all animal studies, uncoated and coated titanium exhibited a more osteogenic behavior than did uncoated PEEK,^{21–24} while comparable bone-implant contact was observed in HA-coated PEEK and coated titanium implants.²¹

DISCUSSION

Osseointegration of implants depends on a number of factors: bone volume, implant geometry, surface topography, systemic health of the patient, and local factors (such as oral hygiene and smoking habits) are all critical for success of implant therapy.²⁵ Implant surface characteristics are vital for instituting primary stability after placement into the bone. It has been observed that presence of surface roughness, at the micrometer and nanometer scales will promote cellular adhesion.² Furthermore, coating of materials such hydroxyapatite and calcium phos-

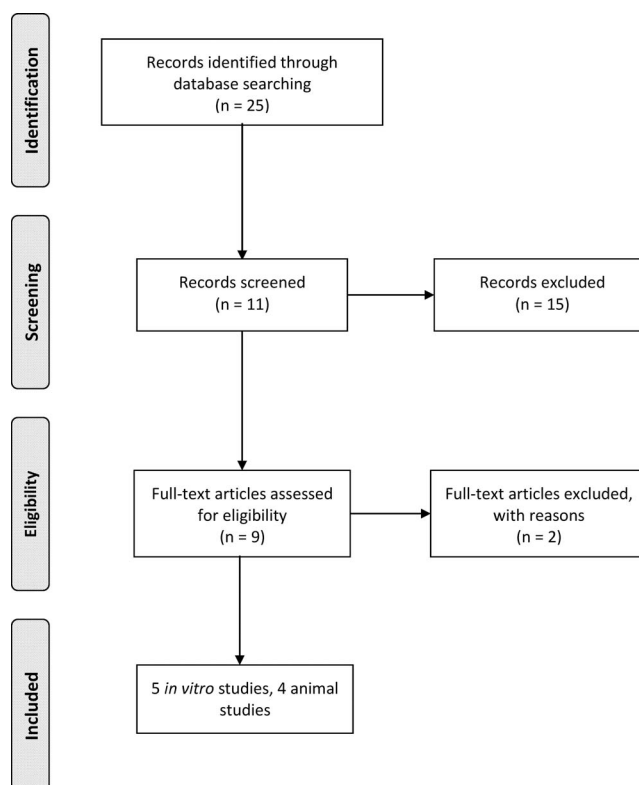


FIGURE. The search methodology employed for this review.

phates on the implant promotes proliferation of osteoblasts.²⁶ Indeed, in studies conducted on titanium implants, surface modification has been observed to enhance bone-implant contact and interfacial bonding to the bone.²⁷ Although a number of modifications of PEEK implants have been described in the literature,^{28,29} very few studies have compared the osseointegration and bioactivity of PEEK implants with titanium.

Sagomyants et al¹⁵ cultured osteoblasts cells, isolated from surgery patients, on the surface of PEEK and titanium implants and then compared cellular proliferation and activity on both implant materials. It was observed that PEEK stimulated proliferation of osteoblasts, mRNA synthesis, and collagen I turnover comparable to those on smooth and rough titanium. This suggested that carbon fiber reinforced PEEK (CFR-PEEK) and titanium stimulated cellular differentiation and proliferation in comparable magnitude. In contrast to a later study by Sagomyants et al, in vitro studies failed to observe any similarities between the bioactivity of PEEK and titanium. In a series of studies by Olivares-Navarrete et al,^{16,18,19} results indicated that although PEEK did stimulate cellular proliferation, the cells proliferating on PEEK were less osteoconductive than those on titanium.¹⁶ As suggested by the increased bone-morphogenetic proteins (BMPs) released by MG63-cells, titanium stimulates a more mature cell growth. Indeed, BMPs have been viewed as indicative of increase bone formation and have been used in regenerative medicine for bone regeneration.³⁰ Formation of new blood vessels (angiogenesis) is important for bone regeneration and successful osseointegration.³¹

TABLE 1
Methodology, duration, control, and test implant materials and conclusions of included in vitro studies*

Authors and year	Methodology	Duration	Implant Material		Main Outcomes
			Control	Test	
Sagomyants et al ¹⁵	Adhesion, proliferation and mineralization assays of human osteoblasts cultured on implant discs	3 weeks	Ti (polished and rough)	PEEK (polished and rough), CFR-PEEK (polished and rough)	Biocompatibility of all samples comparable
Olivares-Navarrete et al ¹⁶	Comparison of bone morphogenic proteins produced from human MG63 osteoblast-like and their phenotype.	24 hours	Tissue culture polystyrene	PEEK, Ti (polished and rough)	More mature osteoblasts observed on Ti
Zhao et al ²⁰	Proteomic analysis of human osteoblast-like MG-63 cells cultured on implant discs	2 weeks	Ti	PEEK	PEEK inhibited mRNA processing leading to lower proliferation of cells
Olivares-Navarrete et al ¹⁸	Comparison of angiogenic factors produced from human MG-63 cells cultured on PEEK and Ti	Not stated	Tissue culture polystyrene	PEEK, Ti (rough and smooth)	Ti promoted production of angiogenic factors more than PEEK
Olivares-Navarrete et al ¹⁹	Comparison of pro-inflammatory and osteogenic factors produced from human MG-63 cells cultured on PEEK and Ti	1 week	Tissue culture polystyrene	PEEK, Ti (rough and smooth)	PEEK promoted fibrotic changes and Ti promoted production of osteogenic factors

*PEEK indicates polyetheretherketone; CFR, carbon fiber reinforced.

Olivares-Navarrete et al also observed increased expressions of endothelial growth factor A, angiopoietin-1, and fibroblast growth factor 2 from cells cultured on titanium as compared to those growing on PEEK.¹⁸ Moreover, they observed that PEEK stimulated a more inflammatory proliferation of cells when compared to titanium. Increased levels of pro-inflammatory interleukins and proapoptotic mRNA produced from cells cultured on PEEK indicated a more fibrotic interaction

between the polymer and bone.¹⁹ That said, titanium was observed to promote a cellular response that is more favorable for bone formation. Proteomic analysis conducted by Zhao et al²⁰ indicated that PEEK favors lesser production of pro-osteoblast proteins than titanium, further strengthening the notion that PEEK is less osseointegrative than titanium.

The results from animal studies support those obtained from the aforementioned in vitro studies. In all the studies,

TABLE 2
Study design, number of animals, duration, site of implantation, control and test implants, and outcomes of the included animal studies*

Authors and Year	Study Design	Animals (n)	Duration	Site of Implantation	Implants		Main Outcomes
					Control (n)	Test (n)	
Koch et al ²⁴	In vivo, prospective, split-mouth	6 dogs	4 months	Mandible	Ti	Zr, Ca-coated Zr, uncoated PEEK	Bone-implant contact significantly lesser around PEEK than other implants
Nakahara et al ²¹	In vivo, prospective	Rabbits†	3 months	Femur	Ti (12), HA-coated Ti (12), CFR-PEEK (10)	HA-coated CFR-PEEK (12)	Interfacial strength of HA-coated CFR-PEEK equal to HA-coated Ti
Webster et al ²²	In vivo, prospective	32 rats	3 months	Skull	Ti (24), PEEK (24)	Si ₃ N ₄ (48)	Si ₃ N ₄ had higher anti-bacterial and osseointegrative properties than Ti and PEEK. Ti osseointegrated more than PEEK
Wu et al ²³	In vivo, prospective	18 sheep	6 months	Vertebrae	PEEK cage (18)	Porous Ti cage (18)	More bone formation observed around Ti

*PEEK indicates polyetheretherketone; CFR, carbon fiber reinforced.

†Number unknown.

lesser bone-implant contact was observed around PEEK than around titanium implants.^{22–24} When Koch et al compared the osseointegration of titanium, coated and uncoated zirconia, and PEEK implants, significantly lesser bone-implant contact was observed around PEEK implants.²⁴ Similar observations were made by Webster et al, who observed a significantly higher susceptibility of bacterial growth on PEEK implant surfaces, which may be an additional factor playing a role against diminished osseointegration of PEEK implants.²² However, more bacterial studies are needed to further investigate this hypothesis. Results from Nakahara et al suggested that the limited osseointegrative properties of PEEK may be overcome by coating it with bioactive materials such as hydroxyapatite.²¹ Titanium, being metallic with a very high melting temperature, can be sprayed using high-temperature processes without degradation of its surface and structure. Unlike titanium, PEEK is a polymer with a low melting point and, therefore, processes such as plasma spraying and acid-etching may have a detrimental effect on the surface and bulk mechanical properties.³² A major cause of concern of uncoated PEEK is its low wettability and, therefore, a high hydrophobicity that may prevent initial cellular adhesion.³³ Although several methods have been advocated for modification of PEEK,²⁹ no studies so far have compared the osseointegration of coated and modified PEEK with commercially available titanium implants.

The studies included in this review had a number of limitations: for instance, the in vitro studies were conducted for short durations.^{15,16,18–20} Results from in vitro tests alone are inadequate to ascertain the safe use of dental implants in the clinical setting, and robust animal studies are required before they be used safely.³⁴ Only 4 animal studies,^{21–24} compared to 5 in vitro studies^{15,16,18–20} were found during the search process, giving us a lack of animal trials comparing osseointegration of PEEK to that of titanium. Furthermore, a number of inadequacies in the study design may have led to biased outcomes. None of the animal studies included statistically predetermined sample sizes.^{21–24} Moreover, neither protocol of randomization or blinding of animals was described.^{21–24} No studies described any animal subjects lost to the experiments.^{21–24} Future studies should focus on improving the study design to minimize the sources of bias. The majority of animal research conducted has focused on PEEK's application in spine and cranial surgery.⁷ Indeed, among the studies reviewed, PEEK implants were placed in the mandible in only one study.²⁴ Macroscopic characteristics, such as implant shape and thread geometry, of PEEK and PEEK-based composites should be studied further and compared to currently used titanium implants. Although coated PEEK may prove to be a viable alternative to titanium, more research should be conducted to analyze the PEEK-apatite bonding, as dental implants are known to fail due to delamination of the coating material.²

Indeed, more studies are warranted to vindicate the use of PEEK in dental implants. There have been published case reports that document failure of uncoated PEEK implants resulting from severe peri-implantitis caused by poor osseointegration.³⁵ Although PEEK dental implants are commercially available (PEEK-Optima and PEEK-Optima HA Enhanced, Invibio, Lancashire, UK), no clinical studies have been conducted to

ascertain the clinical efficacy of PEEK dental implants. Therefore, more animal studies and human trials are vital before PEEK, in any form, is to be used as a dental implant material clinically.

CONCLUSION

Unmodified PEEK is less osseointegrative and bioactive than titanium. Hence, in its unmodified form, PEEK is unsuitable to be used as dental implant. Inadequate osseointegrative and bioactivity of the dental implant may lead to severe implantitis and implant failure. Therefore, significantly more research and long-term trials focusing on improving bioactivity of PEEK are required before it can be used as dental implant. More comparative animal and clinical studies are warranted to ascertain the potential of PEEK to be a viable alternative to titanium.

ABBREVIATIONS

BMPs: bone-morphogenetic proteins

CFR: carbon fiber reinforced

PEEK: polyetheretherketone

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