Universidad Europea VALENCIA

Grado en ODONTOLOGÍA

Trabajo Fin de Grado

SYSTEMATIC REVIEW

Comparison of PEEK to titanium as an alternative material in dental implants

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Abstract

Introduction: The titanium implant has been the gold standard since the last 60 years. It has excellent osseointegration ability attributing to its success. PEEK is a polymer with potential to be an alternative material to titanium implants. It has better aesthetics, better elastic modulus, and better radiographic properties to titanium, however it still lacks sufficient research concerning its osseointegration ability from various surface modifications.

Justification and objectives: The purpose of this study is to report the optimum implant material for osseointegration between PEEK and titanium according to its surface modification. This topic is scarcely researched since PEEK is a new material in implantology.

Material and methods: The search was conducted on Scopus and MEDLINE complete using the following keywords and Boolean operators: ("peek dental implants" AND "polyether ether ketone" AND "surface modification" OR "CFR PEEK dental implants" OR "GFR PEEK dental implants" OR "titanium dental implants" AND "comparison" AND "surface modifications" AND "osseointegration" NOT "zirconia").

Results: 101 articles were produced by the two databases, after systematic processing using the inclusion and exclusion criteria, 10 articles were included in this review.

Conclusion: titanium remains the optimum implant material. The optimum surface modification is SLA for titanium and TiO_2 plasma spray for carbon fibre-reinforced polyetheretherketone-hydroxyapatite. Further long-term animal trials directly comparing titanium and PEEK as well as further research into carbon fibre-reinforced polyetheretherketone-hydroxyapatite would be very recommendable.

Resumen Español

El implante de titanio ha sido el gold standard desde los últimos 60 años. Tiene una excelente capacidad de osteointegración y, por lo tanto, éxito del implante. PEEK es un polímero con potencial para ser una alternativa a los implantes de titanio. Tiene mejor estética, módulo elástico y propiedades radiográficas que el titanio, sin embargo, aún falta investigación sobre su capacidad de osteointegración provocada por modificaciones en la superficie.

El propósito de este estudio es informar sobre el implante óptimo para la osteointegración entre PEEK y titanio e investigar la modificación óptima de la superficie para la osteointegración de PEEK y la osteointegración de titanio. Este tema está poco investigado ya que el PEEK es un material nuevo en implantología.

La búsqueda se realizó en Scopus y MEDLINE utilizando las siguientes palabras clave y operadores boolean: ("peek dental implants" AND "polyether ether ketone" AND "surfacemodification" OR "CFR PEEK dental implants" OR "GFR PEEK dental implants" OR " implantes dentales de titanio" Y "comparación" Y "modificaciones de superficie" Y "osteointegración" NO "zirconia")

101 artículos fueron producidos por las dos bases de datos, después del procesamiento sistemático utilizando los criterios de inclusión y exclusión, 10 artículos fueron incluidos en esta revisión

El titanio sigue siendo el material de implante óptimo. La modificación óptima de la superficie es SLA para titanio y pulverización de plasma de TiO_2 para polieteretercetona-hidroxiapatita reforzada con fibra de carbono. Sería muy recomendable realizar más ensayos en animales a largo plazo que comparen directamente el titanio y el PEEK, así como más investigaciones sobre la polieteretercetona-hidroxiapatita reforzada con fibra de carbono.

1. INTRODUCTION

1.1 Prosthetic dentistry

In modern prosthetic dentistry, we are presented with a range of treatment options to replace absent teeth. Absences can arise as a result of decay, disease and trauma(1) Oral rehabilitation can be achieved through removable dentures, fixed prosthesis or a combination of both.

These options vary according to the patients and dentists' expectations and ability. Influencing factors include budget, oral condition, hygiene, habits, and the indications of each treatment. Each method has its own pros and cons.

Implants are the gold standard treatment; they have great success rates and long-term longevity. Titanium has been the material of choice in implants since the last 60 years. Dentistry is forever seeking to improve upon its previous advances in order to optimise outcome. Concerns with the stiffness of titanium in relation to bone has given way to research for new materials as potential replacements, PEEK being a potential competitor(2).

1.2 IMPLANT ALTERNATIVES

1.2.1 Removable prosthesis

A removable prosthesis is composed of an acrylic base that can be combined with a metal framework for strength. It uses the soft tissue as support for retention aided by clasps, rests and precision abutments (in cases of partial prosthesis). Attached to the acrylic base are the prosthetic teeth. The aesthetic result is usually subpar compared to fixed alternatives. There is incipient and continued bone loss at the edentulous site due to insufficient alveolar bone stimulus (disuse atrophy). Therefore, there is poor long-term retention. It subsequently results in poor mastication and phonation. There is a negative social dogma attached to denture wearing, patients feel embarrassed having to remove the prosthesis daily. Additionally, the bulky and unnatural manner of the prosthesis often causes

taste altercations(3). Lastly, the constant changes and adjustments from the oral tissues require regular follow-ups and adjustments, inconveniencing both the patient and practitioner (2,3).

Regarding popularity, it makes up a significant portion of prosthetic rehabilitation cases. It is usually the cheapest option, especially in cases of more severe tooth loss (more than three teeth). Medical contraindications, economic limitations and negative attitude towards implants are contributory to its adoption (4)

1.2.2 Fixed prosthesis bridge

Fixed partial dentures require preparation of the adjacent teeth. Conventional FDPs require aggressive preparations of adjacent natural teeth. This in turn exposes the sites to secondary caries and irreversible pulpitis(1). In order to avoid iatrogenic damage, as a precaution, adjacent pillar teeth are endodontically treated prior to crown preparation (case dependent). This can compromise the longevity of said pillars. Maintaining sufficient oral hygiene is more difficult due to the fixed manner of the prosthesis along with food retention in the spaces between soft tissue and prosthesis. Over time, there is bone loss at the alveolar crest site below the pontic as a result of disuse atrophy since bone requires masticatory stimulus to maintain volume. To summarise FDPs advantages, they have better aesthetics compared to removable prosthesis, the initial cost cheaper than implants and it doesn't require any surgery to prepare the site (3).

The prosthetic alternatives to implants carry both short term and long-term repercussions. Although they may be more economically feasible, they inevitable demand on going treatments. In both cases, the patient will lose alveolar bone support due to resorption (disuse atrophy) (3).

1.3 Dental implant

The dental implant behaves as a substitute to the tooth root embedded in the alveolar bone. The crown of the tooth is replicated with a prosthesis. It is placed above the implant abutment. In essence, there are three parts to the implant: the body, the abutment and the prosthesis. Once surrounding tissue to the implant

body has healed, it can be combined with a RFD (over denture or hybrid prosthesis) or FDP crown. They can be used to replace a single tooth or the entire arch (3).

Implants solve the shortcomings of the FDP bridges and RPD/RFD dentures. They achieve a similar bite force to natural teeth, whereas the prosthetic alternatives flex to compensate load bearing. Implants do not require preparation of adjacent teeth and give better facial aesthetics than aforementioned prosthetic alternatives. Bone volume is maintained at the alveolar ridge supporting the lip and maintaining facial proportions (3).

Disadvantages of implant placement include financial limitations, medical condition related contraindications (age, pregnancy, bisphosphonate use, diabetes and bone disorders such as Paget's disease) limit their universal applicability.(3)(4)

1.3.1 Success criteria of implants

Alberktson, Zarb, Washington and Erickson et al (6) revised a criterion for implant success. It is stated as follows:

i. Individual unattached implant that is immobile when tested clinically.
ii. Radiograph that does not demonstrate evidence of peri-implant radiolucency.
iii. Bone loss that is less than 0.2mm annually after the implants first year of service
iv. Individual implant performance that is characterised by absence of persistent and/or irreversible signs and symptoms of pain, infections, necropathies, paraesthesia, or violation of the mandibular canal
v. A survival rate of 85% at the end of 5-year observation and 80% at the end of a 10-year observation.(6)

The first three criteria all relate to the bone response in relation to implant placement(6). Bone response post implant placement is synonymous with

osseointegration. It is dependent on both bone quality and implant biomechanics. A conservative surgical preparation and placement is also essential along with sufficient post operatory healing time. Bone quality is another factor determining prognosis of the implant. Human bone has been classified into four categories of density by Lekholm and Zarb (7).

Type I	Spongy trabecular centre and thick outer cortical bone
Type II	Dense trabecular centre and thick outer cortical bone
Type III	Dense trabecular centre and thin outer cortical bone
Type IV	Spongy trabecular centre and thin outer cortical bone

Type II and type III have better load bearing capacity thus creating favourable stability and quicker healing time. The anterior region of both the maxilla and mandible have thicker cortical and denser trabecular bone in comparison to posterior regions(7).

1.3.2 Osseointegration

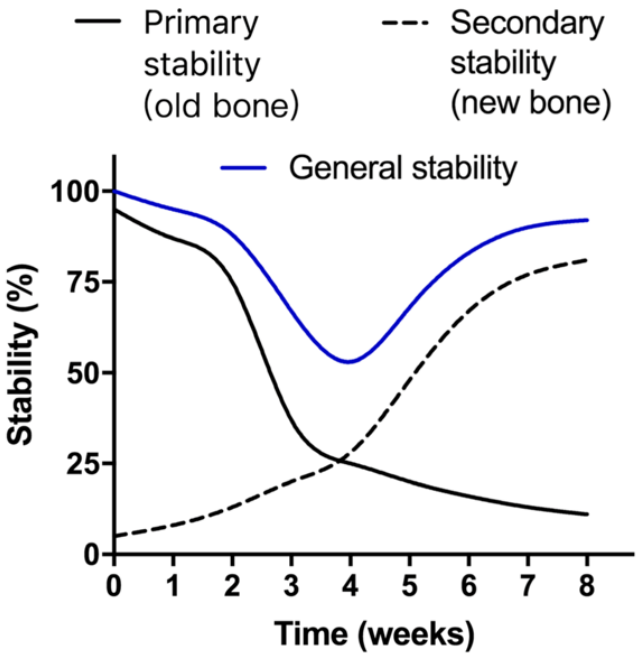
Osseointegration can be comprehensively defined as “the process resulting in direct structural and functional connection between ordered, living bone and the surface of a (load bearing) implant” (7). Osseointegration can be measured by the clinician via resonance frequency devices. It is a tool that permits the clinician to estimate the stability of the implant, the unit of measurement is ISQ (implant stability quotient) the scale goes from 0-100, a higher value representing more stability(8). To gain optimal anchorage and mechanical stability, direct bone to implant contact is required (BIC), providing the basis for desired dental implant functioning (7)

When the implant is inserted, mechanical stability is achieved, also known as primary stability. The surgical bone preparation is created smaller than the implant diameter ensuring a tight fit upon insertion. Consequently, blood fills the gaps between the implant threads along with inflammation products. At this stage, there is a purely mechanical fit without any biological interference. Primary stability is dependent on surgical proficiency, implant design (threaded or

cylindrical) and bone quality. Primary stability is critical to determine the long-term success of the implant.

During the healing phase after the blood clot is formed between implant and bone, a biological connection is formed with parallel fibred bone and lamellar bone formation. This remodelling phase is continuous, from 6-12 weeks at the peri implant location. This is called secondary stability, also known as osseointegration. Here is where BIC is achieved.

Primary stability decreases over time as secondary stability increases. After the four-week period, stability is at its lowest, it then recovers when new bone formation commences. (7)



(Figure 1)(7)

Figure 1 displays the relationship between primary and secondary stability in relation to the two-month healing period after implant placement.

1.3.3 Biocompatibility and biomechanics of the ideal implant material

Biocompatibility refers to the intrinsic nature of the material to perform appropriately to a specific application. ADA have outline 5 acceptance guidelines for biocompatible implant materials:

1. Evaluation of physical properties ensuring sufficient strength
2. Demonstration of ease of fabrication and sterilization potential without material degradation
3. Safety and biocompatibility evaluation, including cytotoxicity testing and tissue interface characteristics
4.Freedom from defects
5. At least two independent longitudinal prospective clinical studies investigating efficacy (9)

For an implant material to be accepted as biocompatible they must be able fulfil thess criterion.

Force produced during mastication on the natural teeth can average between 500-800N depending on the tooth, posterior teeth absorb more force than anterior. Implants must distribute this force equally to the bone. Natural teeth have a periodontal ligament whereas implants do not, it is a thin collagen sheath that distributes forces along the cortical bone (10). To create an even distribution of forces on the cortical bone from the implant, the material must have an elastic modulus similar to bone (15 gpa) (11). When there is a discrepancy between the elastic modulus of the implant and bone marginal bone loss can occur, it is one of the most important causes of long-term failure of dental implants (11).

This phenomenon is called stress shielding, formerly described as Wolf´s law. Bone will adapt to the load bared upon it. Rigid materials transfer less stress, leading to loading pressure toward the implant and not toward the bone. As a result, it will cause peri implant bone resorption (12).

The elastic modulus is calculated by the ratio of elastic stress to elastic strain. It describes the stiffness of a material relating to its fatigue strength. The optimal implant material has similar elastic modulus to bone and high fatigue resistance(12).

1.4 Titanium as an implant material

Titanium is a metal; it is a transitional element in group 4 of the periodic chart. It was first introduced in dentistry at the end of 1960 by Branemark and has since been the gold standard for implants (13,14) Ti6AL4V is the most researched titanium alloy, It is used in orthopaedic dentistry due to its relatively lower elastic modulus (15).

Titanium has a wide range of biomedical applications including dental implants, joints, screws, bone plates and cardiovascular devices. This is thanks to its great biocompatibility; it is relatively inert and corrosion resistance. These accolades contribute to its high osseointegration success (13,14).

Its inertness is a result of the metals passivity. Passivation is defined as the process of transforming a chemically active surface of a metal to a less active surface (9). Titanium will react with oxygen to form TiO_2 readily in air. It can also reform this oxide protective layer in vivo; it reduces corrosion rate and the oxidising layer can be maintained over long term fatigue also. Over long periods of time, this oxide layer can theoretically be penetrated when factoring in acidic conditions, such as inflammatory bouts at the mechanical wear sites (16).

The surface modification techniques for titanium can also jeopardise its mechanical strength, potentially exposing the implant body to micro fracturing thus breaching its oxide layer. The metal ions are released after corrosion events (Ti+, Co+, Al+). There have been reports of these carcinogenic trace metal ions being found in the liver, lymph nodes, blood and lungs. Consequently, they can promote periimplantitis by creating negative cascading effects on macrophage activity, inflammation and bone resorption. There have been reports of titanium causing allergic and hypersensitivity reactions as a result of the mentioned leakage(11,16).

Titanium surface modifications are split into mechanical and chemical methods. Mechanical methods include plasma spray and sand grit blasting method. Chemical methods include etching, anodization, and antibacterial coating(14).

Titanium can be etched by strong acids (hydrochloric acid, sulfuric acid, nitric acid and hydrogen fluoride). It is utilized to produce increased surface roughness; in this case it will produce a roughness of 0.5 to 2 micrometre(14).

Anodization implements acid etching in combination with electrical impulses to partially dissolve the oxide layer and substitute it with ions derived from the acids. The antibacterial coatings reduce inflammation responses experienced during the healing phase. This creates a better environment for bone to implant contact due reduced connective tissue volume (14)

There are also concerns of titanium's aesthetic outcome, for example, in cases of patients with thin biotype mucosa, a grey colour can become visible (11). Even in cases of peri-implant resorption or gingival recession, the neck would reveal grey hue of titanium. Resorption can arise as a result of titanium's high modulus of elasticity compared to bone. It is more than 7x higher (110 gpa compared to 15 of cortical bone)(11). As mentioned earlier the disparity can give rise to stress shielding. It is especially present in the junction between the prosthesis and implant body. This can develop into further resorption and subsequent implant failure. It also gives scattered images during radiographic analysis, making radiographic diagnosis more difficult for the dentist. (11,12,17)

1.5 PEEK as an implant material

PEEK was developed in 1978 by a group of English scientists(12). It is a high-performance polymer, being a member of PAEK (polyarylether ketone) polymer family. It is a semi crystalline polycyclic linear aromatic structure(18). Essentially it falls under the category of a plastic.(19) Due to Its excellent biocompatibility, there has been no reports of cytotoxicity or adverse reactions. It has been used in the field of orthopaedic devices and traumatology to replace hard tissues. PEEKs use profile crosses that of titanium'. Its original industrial sector use includes aircrafts, automotive and electronics. In dentistry it can be applied in removable prosthesis (framework and artificial teeth), fixed bridges and crowns

and implants (20). It has thermal stability above 300c high mechanical resistance, high physical resistance, and water resistance (18,19,21).

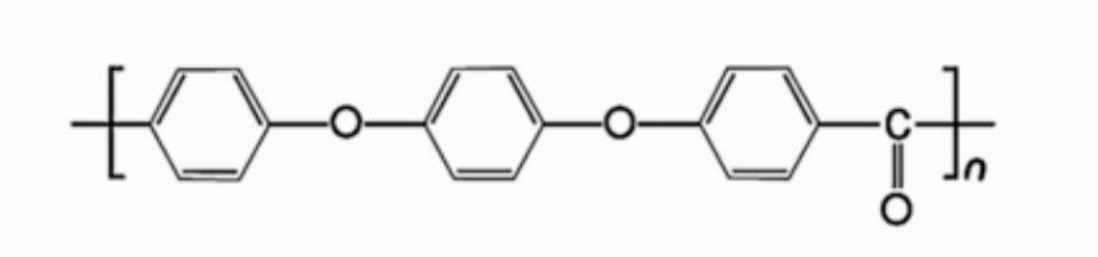


figure 2 displays the chemical structure of PEEK (19)

PEEK has become an increasingly popular researched implant material alternative. It solves the issues presented by titanium. It can meet aesthetic requirements; its colour is closer to that of bone. Its elastic modulus is closer to that of cortical bone also (pure form 3-4 gpa) and it can be reinforced with to carbon fibre or glass (12 gpa and 18 gpa respectively). Therefor being more stress protective. (11,21)

1.6 PEEK surface modifications

To create better osteogenic potential PEEK has undergone various surface modifications. It doesn't have the advantage of passivity obtained by titanium, giving pure PEEK limited bioactivity(12). Titanium dioxide and hydroxflourapatite sprays have been utilised as a technique to achieve superior osseointegration potential. Acid etch systems have also been used to increase surface roughness (21)

Surface modifications and their pertinence to osseointegration will be explored in more depth throughout the course of this systematic review.

2. JUSTIFICATION, HYPOTHESIS AND OBJECTIVES

2.1 Justification

Dentistry has always strived to discover and create better materials to fulfil existing pitfalls of existing materials. Titanium has been the gold standard for implants since the last 60 years, it does however come with its relative disadvantages. PEEK in comparison is a new material which has potential to replace titanium as it claims more suitable properties. Both the patient and dentist can benefit from its proposed advantages. For the dentist, gaining knowledge of PEEKs potential will help make more informed decisions regarding material choice. This review aims to bring further awareness to the capabilities of PEEK materials in the world of implant biomaterials.

2.2 Hypothesis

PEEK is a more suitable material in comparison to titanium as an implant body in relation to its compatibility with cortical bone due to its biomechanical properties and success rate.

2.3 Objectives

Main objective:

- Reporting the optimum material for implant osseointegration (between PEEK and titanium).

Specific objectives:

- To investigate the optimum surface modification for titanium osseointegration.

- To investigate the optimum surface modification for PEEK osseointegration.

3. MATERIALS AND METHODS

The PRISMA guidelines has been followed to prepare this systematic review(22).

3.1 Eligibility criteria

a. Protocol and focused question

Population (P)	Dental patients treated with endosseous implants
Intervention (I)	PEEK materials as the implant body
Comparison (C)	Titanium as the implant body material
Outcome (O)	Increased osseointegration according to parameters (BV/TV, BIC or BA)

In dental patients treated with endosseous implants, do PEEK materials have better osseointegration compared to titanium as an implant body material?

b. Inclusion and exclusion criteria

Inclusion criteria

- Type of article: Published within the last 10 years (up to 2012) and in English

Exclusion criteria

- in-vitro studies not including in vivo experiments, studies without BV/TV, BIC or BA variables.

3.2 Information sources and search strategy

3.2.1 Databases

The following two data bases were used to perform the article search:

- MEDLINE complete
- SCOPUS

3.2.2 Construction of the search algorithm

Boolean operators “AND”, “OR” and “NOT” were utilized to compose the search algorithm, the following sequence shows the order in which the key words were composed:

(“peek dental implants” AND “polyether ether ketone” AND “surface modification” OR “CFR PEEK dental implants” OR “GFR PEEK dental implants” OR “titanium dental implants” AND “comparison” AND “surface modifications” AND “osseointegration” NOT “zirconia”)

Date of the last search: 05/03/22

Manual searches or cross references were not utilized to retrieve further articles.

Data base	Search algorithm	Filters	Date
Medline complete	(“peek dental implants” AND “polyether ether ketone” AND “surface modification” OR “CFR PEEK dental implants” OR “GFR PEEK dental implants” OR “titanium dental implants” AND “comparison” AND “surface modifications” AND “osseointegration” NOT “zirconia”)	2012-2022 And Articles in English	5th March, 2022
SCOPUS	(“peek dental implants” AND “polyether ether ketone” AND “surface modification” OR “CFR PEEK dental implants” OR “GFR PEEK dental implants” OR “titanium dental implants” AND “comparison” AND “surface modifications” AND “osseointegration” NOT “zirconia”)	2012-2022 And Articles in English	5th March, 2022

3.3 Selection process

Firstly, the duplicate articles were removed. Following this, the remaining titles and abstracts were revised to satisfy pertinence and only articles referring to the implant body were selected (not to the implant crown or abutment). Thereafter, the eligibility criteria were applied through full-text assessment.

3.4 Data collection process

Included studies were summarise into two tables: general characteristics of included studies and results of included studies

General characteristics followed according to the titles: country, type of study, sample size, animal studied, mean age, study groups (control and test), time until sacrifice, study variables and risk of bias

Results of included studies followed according to the titles: author and year, implant material, surface modification control, surface modification control, implant design, BIC, BV/TV, Bone area and statistical significance.

3.5 Quality assessment

Each study included in this systematic review was screened using the CASPe (critical appraisal skills program) checklist(23). It serves as checklist guide for each article being comprised of 12 specific criteria. The studies are filtered through these criteria being categorised into “yes”, “no” or “cannot tell”. Lastly, each study receives a score unto 12 to provide a quantitative value of their methodological quality.

4 RESULTS

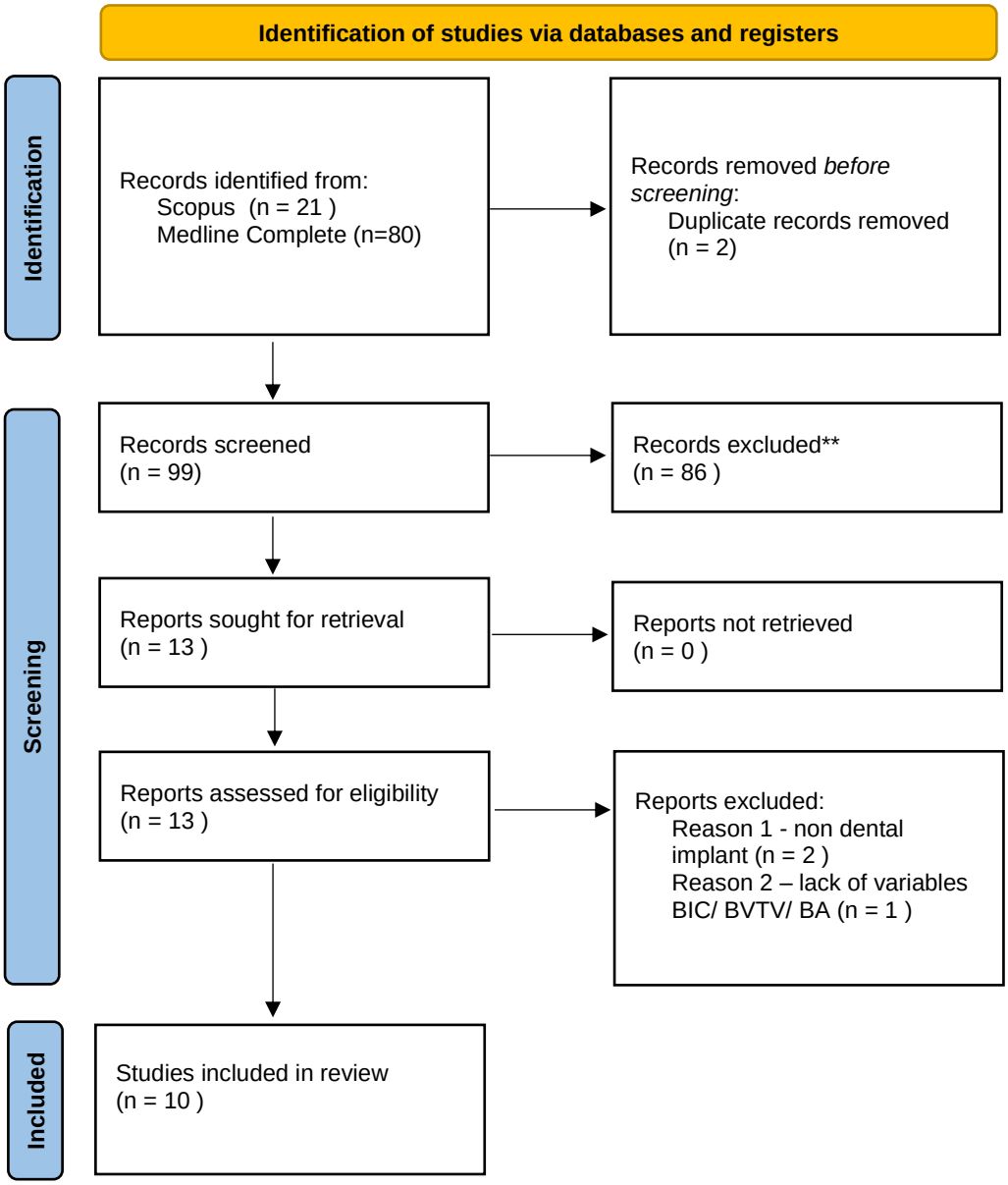


Figure 1: Flowchart of the selection process of articles for the systematic review.

Table I: CASPe checklist for randomised control trials

	Wulin He 2019	Young-Sun Hong 2014	Eugenio Velasco-Ortega 2019	Won-Tak Cho 2021	Ping-Jen Hou et al. 2017	Guanglong Li 2016	Zhiquang Xue 2020	Maihemuti Yakufu 2020	Xiao Xu 2018	Anxiu Xu 2014
1. Did the study address a clearly focused research question?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was the assignment of participants to interventions randomised?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Were all participants who entered the study accounted for at its conclusion?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. 4. Were the participants 'blind' to intervention they were given? Were the investigators 'blind' to the intervention they were giving to participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Were the people assessing/analysing outcome/s 'blinded'?										
5. Were the study groups similar at the start of the randomised controlled trial?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6. Apart from the experimental intervention, did each study group receive the same level of care?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Were the effects of intervention reported comprehensively?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8. Was the precision of the estimate of the intervention or treatment effect reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9. Do the benefits of the experimental intervention outweigh the harms and costs?	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
10. Can the results be applied to your local population/in your context?	Y	N	N	Y	Y	Y	Y	Y	Y	Y
11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	Y	N	N	Y	Y	Y	Y	Y	Y	Y

Table II: General characteristics of included studies

Author/ Year	Country	Type of study	Sample			Study groups		Time until animal sacrifice (weeks)	Study variables	Risk of bias
			Sample size	Animal studied	Mean age (months)	Control	Test			
Wulin He et al. 2019 (24)	China	Randomized Controlled Clinical Trial	4	Beagle dog	12	16	8	12	BIC (mean %) BV/TV (mean mm) BA(mean %)	LOW
Young-Sun Hong 2014 (25)	Korea	Randomized Controlled Clinical Trial	3	Rabbit	18	3	3	1	BIC (mean %) BA (mean %)	MEDIUM
Eugenio Velasco-Ortega 2019 (26)	Spain	Randomized Controlled Clinical Trial	6	Rabbit	6.5	12	12	12	BIC(mean %) BV/TV (%)	LOW
Won-Tak Cho 2021 (27)	Korea	Randomized Controlled Clinical Trial	6	Beagle dog	36	12	24	8	BIC(mean %) NBA	LOW
Ping-Jen Hou et al. 2017 (28)	Taiwan	Randomized Controlled Clinical Trial	6	Mini pig	12	6	6	8 and 12	BIC (mean %)	LOW

Guanglong Li, 2016 (29)	China	Randomized Controlled Clinical Trial	12	Beagle dog	12	12	24	6	BIC % NBA	LOW
Zhiqiang Xue al.2020 (30)	China	Randomized Controlled Clinical Trial	15	Rat	6	15	15	6	BV TV %	LOW
Maihemuti Yakufu 2020 (31)	China	Randomized Controlled Clinical Trial	10	Rat	3	10	10	2 and 4	BV TV %	LOW
Xiao Xu 2018 (32)	China	Randomized Controlled Clinical Trial	3	Beagle dog	18 months	8	8	8	BV/TV %	LOW
Anxiu Xu 2014 (33)	China	Randomized Controlled Clinical Trial	6	Beagle dog	18 months	6	18	4	BV/TV **%**	LOW

Table III: Results of included studies

Author and year	Implant material	Surface modification control	Surface modification test	Implant design	BIC (%)	BV/TV (%)	Bone area (%)	Statistical significance
Wulin He et al. 2019 (24)	Titanium	large-grit sandblasting and acid etching (SLA) micro arc oxidation (MAO)	large-grit sandblasting combined with micro-arc oxidation **(**SL-MAO**)**	Ø 3x10mm Rod shaped Femur	MAO = 43 SL-MAO =52 SLA = 60	MAO= 57 SL-MAO= 68 SLA= 78	MAO= 70 SL-MAO= 80 SLA= 85	Statistical significance between SL-MAO and SLA/MAO in both BIC and BA respectively
Young-Sun Hong 2014 (25)	Titanium	F-mod	modSLA	F-mod Ø3.5mmx11mm modSLA Ø3.3mmx10mm Tibia	F-mod = 34.4 modSLA = 36.9	-	F-mod = 34.8 modSLA = 42.6	No statistical significance
Eugenio Velasco-Ortega 2019 (26)	Titanium	Acid etched with sand blasting treatment (SA)	Oxidised implant surface (OS)	SA = Ø 4x10mm OS = Ø 4.1x10 mm	SA = 53.49 OS = 50.94	SA Cervical 41 Medial 30 apical 42 OS	-	No statistical significance

				Femoral condyle		Cervical 39 medial 20 apical 48		
Won-Tak Cho 2021 (27)	Titanium	Non-treated sandblasted acid etched (SLA)	SLA with Crosslinking collagen type I gamma rays (GR) SLA with Crosslinking collagen type I glutaraldehyde (GA)	Ø 4x8mm Mandibular bone	SLA = 47.3 GA = 54.6 GR = 60.2	-	SLA = 38.2 GA = 43.8 GR = 52.3	No statistical significance in bone area BIC was significantly greater in the GR group than in the SLA group
Ping-Jen Hou et al. 2017 (28)	Titanium	M-Ti Untreated titanium	MST-Ti optimal micro-arc oxidation surface-treated titanium	Ø 3.5x8mm Mandible bone	Week 8 M-Ti = 70.0 MST-Ti = 76.9 Week 12 M-Ti = 71.8 MST-Ti = 88.1	-	-	Statistically significant at 8 weeks and 12 weeks
Guanglong Li, 2016 (29)	Titanium	Micro arc oxidation MAO Ti unmodified	Micro arc oxidation reduced. In alkali solution MAO-AK	Ø 3x10m	MAO = 55.9	-	MAO = 20.6	BIC and NBA statistically

				m rod shaped Left femur	MAO-AK = 32.8 Ti unmodified = 10.4		MAO-AK = 37.0 Ti Unmodified = 13.3	significant for MAO-AK group compared to MAO
Zhiquang Xue et al. 2020 (30)	PEEK	Bare peek	PEEK/CaP-GS*3 PEEK/CaP-GS*6 PEEK/CaP-GS*9	Ø 2x5mm Femur	-	Natural PEEK = 8.5 PEEK/CaP-GS*3 = 11 PEEK/CaP-GS*6 = 15 PEEK/CaP-GS*9 = 15.5	-	Compared with natural PEEK implants, PEEK/CaP-GS groups have significantly higher BV/TV
Maihemuti Yakufu 2020 (31)	PEEK	Bare PEEK	Osteogenic growth peptide PEEK (OGP)	Ø2x6mm Tibia	-	2 weeks Peek = 7 Peek OGP = 27 4 weeks Peek = 11	-	Results between peek and peek OGP are statistically significant Results between PEEK OGP at two weeks and four

						Peek OGP = 28		weeks are also statistically significant.
Xiao Xu 2018 (32)	PEEK	Bare peek	Dexamethasone plus minocycline-loaded liposomes with polydopamine coated PEEK (dex/mino)	Ø4x7mm femur	-	PEEK = 9 PEEK DEX MINO = 27	-	Difference is statistically significant
Anxiu Xu 2014 (33)	PEEK	Pure titanium	carbon fiber-reinforced polyetheretherketone nanohydroxyapatite biocomposite(PEEK/n-HA/CF) plasma-modified micro-structured (p-m-PEEK/n-HA/CF) plasma- modified smooth (p-PEEK/n-HA/CF)	Ø 4x7mm 3rd 4th premolar	-	Ti = 47.5 PEEK/n-HA/CF = 46 p-PEEK/n-HA/CF = 49 p-m-PEEK/n-HA/CF = 58	-	BV/TV is significantly highest in p-m-PEEK/n-HA/CF

5 DISCUSSION

Titanium is the gold standard currently in dental implants since the last 60 years. It has excellent osseointegration due to its passivity, readily oxidising to create a TiO_2 surface layer. This oxide layer promotes osseointegration and maintains surface inertia(2). Osseointegration is defined as “the process resulting in direct structural and functional connection between ordered, living bone and the surface of a (load bearing) implant” and is paramount for implant success(7). Methods of preparing titanium surfaces include mechanical methods such as sand blasting and chemical methods such as micro arc oxidation(14). Titanium’s disadvantages are related to its colour, radiopacity, and long-term apical bone resorption resultant of stress shielding(11,12,17) . Peek on the other hand has excellent structural properties. It has similar elastic modulus to bone avoiding stress shielding. It is not radiopaque, nor does it produce any scattering effect in the radiograph(11,21). The colour can match bone creating better aesthetics, especially in the anterior sector. However, due to PEEKs highly inert surface and lack of passivity, the osseointegration is poor in unmodified surfaces. It requires surface modification to promote osseointegration(12). If this can be achieved, along with is established structural benefits. It could be a competitive alternative to titanium implants.

Eight out of ten studies use BV/TV. it is defined as bone volume per tissue volume. It is calculated by dividing the area of bone volume by the tissue volume in the area of interest (Eugenio Velasco-Ortega et al. (24)). It is given as a percentage and serves as the primary dependant variable since it is found in both titanium and PEEK articles. Bone implant contact (BIC) is the second variable of importance serving as a mediator among titanium articles only. Bone area (BA) is the last dependant variable and is found in four titanium articles, it also serves as a mediator among titanium articles only.

5.1 Titanium surface modifications

Wulin He et al.(25) compared the osseointegration of Micro arc oxidation (MAO) and large grit sand blasting and acid etch (SLA) as two the control groups achieving 60% and 78% BV/TV respectively. Large grit sand blasting combined with acid etch (SL-MAO) achieved 68% BV/TV in the test group. Eugenio Velasco-Ortega et al. (24)also investigated a sand blasting technique (SA) as the control group reporting less the surface roughness from the SEM measurements, 1.74um (SA) versus 2.13um (SLA). Similarly, shown in both the BIC and BV/TV results, the sand blasting method was superior to the oxidised test group in Eugenio Velasco-Ortega et al. (24)(25)The oxidised test group (OS) had the lowest roughness at 1.37um surface roughness. This suggests roughness is has a positive correlation to BV/TV%.

However, the results were not statistically significant between OS and SA neither in BIC results nor in the BV/TV results in the study conducted by Eugenio Velasco-Ortega et al(24). There were different implant designs for the control group (SA) and the oxidised test group (OS), this could also affect the statistical significance of the results.

Young-Sun Hong et al.(26)and Won-Tak Cho et al.(27)both conducted experiments with modified SLA surface modifications on titanium. Young-Sun Hong et al.(26) demonstrated similar outcomes of modified SLA being superior to its control group however the statistical differences were not significant. This perhaps could be due to the implant designs being different, the healing period was only one week or the lack of test subjects. One week is not sufficient to allow for osseointegration (see figure 2). To conclude, better results were attained in Wulin He et al. (25) experiments with unmodified SLA (Bone area 85%) compared to GR, GA, and mod SLA (Bone area 52%, 43.8%, 42.6% respectively)

Won-Tak Cho et al (27)and Wulin He et al.(25)had similar sample sizes and the same animal test subjects. The BIC% results (GR 60.2% (27)BIC SLA 60% BIC (25)) are very similar but the bone area % is higher in Wulin He et al.(25).

Ping-Jen Hou et al.(28) achieved the highest BIC value recorded amongst the titanium BIC results 88.1% at 12 weeks. This study only measured BIC% as the only indicator for in vivo osseointegration. The control group was unmodified titanium (M-Ti). The unmodified titanium also achieved very high BIC values, the second highest in all the titanium BIC percentages. This reduces the credibility of Ping-Jen Hou et al. (28), in the study conducted by Guanglong Li et al.(29) we can see the untreated titanium was credited with a BIC percentage of 10.4% almost 7x lower than untreated titanium result of Ping-Jen Hou et al.(28). It was the only experiment to use mini pigs as the test subjects perhaps contributory to its high osseointegration. Furthermore, there is no bone area nor BV/TV to compare against other studies therefor we will isolating the result as an potential outlier.

The most accurate and reliable study is Wulin He et al.(25), it combines SLA MAO and SL-MAO into one article under the same conditions. It shows statistical significance between each dependant variable and includes all three BIC, BV/TV and BA. The healing time given to the subject was 12 weeks, this complies best with osseointegration opposed to 8 weeks or less.

5.2 PEEK surface modifications

In the PEEK studies, BV/TV was the only osseointegration dependant variable, the control group for three out of four studies was bare PEEK or nature PEEK, also known as untreated peek. The BV/TV values indicate clearly that it is not comparable in its raw form against titanium (Zhiqiang Xue et al.(30) 8.5% BV/TV, Maihemuti Yakafu et al.(31) 11% at four weeks BV/TV, Xiao Xu et al.(32) 9% BV/TV. Anxiu Xu et al.(33) control group is a fourth is a structurally enhanced modified peek. More specifically, carbon fibre-reinforced polyetheretherketone-hydroxy apatite (PEEK/n-HA/CF). unmodified PEEK/n-HA/CF achieved a BV/TV percentage of 46%, significantly higher than bare PEEK.

Dexamethasone is a glucocorticoid; it is intended to reduce the post-operatory inflammation developed after implantation. Xiao Xu et al. (32). Minocycline is a broad-spectrum antibiotic, it serves to modulate cell inflammatory response and discourage bacterial colonization in vitro. The surface roughness achieved was

3.5 um. Although the results were clearly significant against the bare peek control group, 9% and 27% BV/TV, the dex/mino group did not achieve BV/TV levels close to that of titanium (58-78%) by Wulin He et al.(25).

Maihemuti Yakafu et al.(31) osteogenic growth peptide to PEEK surface to create PEEK- OGP. The BV/TV values for PEEK OGP were 27% and 28% at 2 weeks and 4 weeks respectively. It has shown similar results to dex/mino PEEK (32), demonstrating its effectiveness over bare unmodified PEEK. Nonetheless, the BV/TV percentages were not as high as titanium SLA(25). Although, the healing period was only 2 and 4 weeks after implantation. Perhaps the BV/TV% could be higher with a longer healing period.

Zhiqiang Xue et al. (30) experimented with an antibiotic derived surface modification. A combination of gentamycin sulphate, which is a low toxicity broad spectrum antibiotic, and biocompatible calcium phosphate. They are combined and incorporated onto the surface of bare peek by layer-by-layer technique. Despite theoretical potential of the surface modification, practically it revealed poor results regarding osseointegration. BV/ TV percentages ranged from 11% to 15.5% between 3,6 and 9 layers. In comparison with bare peek there is a clear difference, however when comparing to the other antibiotic derived group (dex/mino PEEK) from Xiao Xu et al.(32) it is inferior. It was the weakest result of the four PEEK studies.

Anxiu Xu et al. (33) fabricated a carbon fibre reinforced hydroxy apatite-PEEK (PEEK/n-HA/CF). Three test groups were evaluated: unmodified (PEEK/n-HA/CF), plasma coated (p-PEEK/n-HA/CF) and TiO_2 plasma coated (p-m-PEEK/n-HA/CF). Unmodified Titanium was the control group. At a healing period of only 4 weeks, p-m-PEEK/n-HA/CF showed great potential achieving a BV/TV value of 58% and being statistically significant to all three groups. Differences between unmodified Titanium, PEEK/n-HA/CF and p-PEEK/n-HA/CF were not statistically significant. The experiment was conducted well, the control group was especially pertinent since the PEEK material could be compared directly against unmodified titanium. Anxiu Xu et al. (33) achieved the highest BV/TV percentage compared to the four PEEK materials studied. Macroscopically it has been enhanced, the elastic modulus is closer to human bone when PEEK is

combined with carbon fibre. This technique amalgamates both superior qualities of PEEK and titanium- it provides excellent elastic modulus and the TiO_2 spray forms an oxidised layer bringing adhesion and rugosity (3.19 um)(33).

When comparing BV/TV% of p-m-PEEK/n-HA/CF to BV/TV% of SLA titanium there is a difference of 20% (25), however p-m-PEEK/n-HA/CF had a healing period of 4 weeks and SLA titanium had a healing period of 12 weeks. We have seen in study conducted by Ping-Jen Hou et al.(28) that the difference between 8 and 12 weeks in BIC% reveals statistically significant results. If the p-m-PEEK/n-HA/CF study was repeated with longer healing period (12 weeks) the BVTV% is likely to be higher, thus making p-m-PEEK/n-HA/CF a potential competitor to the SLA titanium in the Wulin He et al.(25) study.

A systematic review by Sunil Mishra et al.(34) evaluated PEEK materials as an alternative to titanium in dental implants. The article aimed to compare PEEK materials to titanium in implants generally. It did not solely focus on the surface modifications and relate them to osseointegration. It investigated PEEK as an abutment screw/crown, peek as a dental implant and surface treatments of PEEK to enhance osseointegration. Sunil Mishra et al.(34) concluded by stating the limitations of PEEK research, highlighting the lack of studies, and emphasising more importance on relating surface modifications to osseointegration. Further research and more controlled clinical trials are required in the future.

5.3 Limitations

Since there is little research conducted on both surface modifications in implantology and PEEK in and around itself, the in-vivo portion of the studies were conducted as animal studies. The search conducted did not reveal studies comparing PEEK and titanium directly, therefor, correlating variables had been compared to determine the individual osseointegration potential of each surface modification, amongst common dependant variables.

The limitations of this study mainly relate to lack of information available in literature regarding surface modifications in implantology and PEEK as implant body. Hence the reason for animal studies in place of human trials. Within animal

studies, there are no follow up trials, the animals are sacrificed and the bone around the implant is harvested to be evaluated. This makes measuring stress shielding phenomenon or measuring secondary effects non-viable as the implant is only tested up to 12 weeks.

The studies collected lacked universal uniformity, it was not possible to find different studies following the exact same surgical technique and methodology. Secondly, only one study contained both titanium and PEEK under the same conditions (Anxiu Xu et al(33)). Implant design in some studies could not be matched, for example, the study conducted by Eugenio Velasco-Ortega et al.(24) had different implant designs between the control group and the test group. Healing time is another variable that greatly varied between studies, Ping-Jen Hou et al. (28) demonstrated that the difference in results from 8 to 12 weeks was statistically significant. Anxiu Xu et al (33) had a healing time of 4 weeks only, the PEEK study had potential to achieve better results.

Only two studies had more than 10 test subjects, this negatively affects the repeatability of the experiments. Animal species is another modifiable factor that was not kept constant throughout, for example, Ping-Jen Hou et al. (28) had abnormally high BV/TV% for unmodified titanium. It could be due to the mini pig subjects since it was the only experiment tested on that species.

Implant location is another modifiable factor not kept constant throughout the experiments. Only two studies implanted into the mandibular bone (being the most appropriate location). All the aforementioned factors influence the final osseointegration result, especially since implant placement is very sensitive to its host, location, and healing environment.

Lastly, only one of the ten articles measured all three dependant variables (BV/TV, BIC, BA) (Wulin He et al.(25)). The PEEK studies only provided BV/TV as the osseointegration dependant variable. This made it especially difficult to provide repeatability in this systematic review since there is only one variable to compare against. Among the titanium articles, BA and BIC variables showed positive correlation comparing to BV/TV, making the BV/TV% a reliable marker for osseointegration.

5.4 Implications

Carbon fibre-reinforced polyetheretherketone-hydroxyapatite (PEEK/n-HA/CF) had the best osseointegration result among the PEEK studies, compared to titanium with SLA surface modification it is still inferior. Further studies need to compare PEEK/n-HA/CF to titanium SLA under the same conditions to extract a definitive conclusion including all three osseointegration variables. Since it is a new material more research must be conducted until it can be used in patients, it has shown potential for high osseointegration success when compared to titanium.

5.5 Future investigations

Long-term animal studies directly comparing the osseointegration of PEEK and Titanium would be incredibly useful. This would ensure both materials are under the same conditions, focusing on its in vivo ability including all three variables (BV/TV, BIC, and BA).

6 CONCLUSIONS

When considering surface modification or osseointegration in terms of implant success between titanium and peek, after reading and comparing multiple articles in the systematic review, we conclude that:

1. Titanium remains the optimum implant material versus PEEK
2. TiO_2 plasma treatment was the best performing surface modification for PEEK, specifically carbon fibre-reinforced polyetheretherketone-hydroxyapatite (PEEK/n-HA/CF)
3. SLA titanium is the best performing surface modification for titanium

Further long-term animal trials directly comparing titanium and PEEK as well as further research into carbon fibre-reinforced polyetheretherketone-hydroxyapatite would be very recommendable.

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ANNEX 1: Prisma checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 13
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 13
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 14
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 15
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 15
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 16
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 16
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 16
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	-
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 16
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	-
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	-
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 16
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	19-21
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	19-21
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 18
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 18
Study characteristics	17	Cite each included study and present its characteristics.	Page 22-23
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 22-23
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 24-28
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 22-23
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis	Page 22-23

Section and Topic	Item #	Checklist item	Location where item is reported
		assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 22-23
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 28-33
	23b	Discuss any limitations of the evidence included in the review.	Page 32
	23c	Discuss any limitations of the review processes used.	Page 32
	23d	Discuss implications of the results for practice, policy, and future research.	Page 33
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	-
Competing interests	26	Declare any competing interests of review authors.	-
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

ANNEX 2: Article format

Comparison of PEEK to titanium as an alternative material in dental implants: A systematic review

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Abstract

Background: The titanium implant has been the gold standard since the last 60 years. It has excellent osseointegration ability and therefor implant success. PEEK is a polymer with potential to be an alternative to titanium implants. It has better aesthetics, elastic modulus, and radiographic properties to titanium however it still lacks research around its osseointegration ability brought about by surface modifications.

Material and methods: The search was conducted on Scopus and Medline complete using the following keywords and Boolean operators: (“peek dental implants” AND “polyether ether ketone” AND “surface modification” OR “CFR PEEK dental implants” OR “GFR PEEK dental implants” OR “titanium dental implants” AND “comparison” AND “surface modifications” AND “osseointegration” NOT “zirconia”)

Results: 101 articles were produced by the two databases, after systematic processing using the inclusion and exclusion criteria, 10 articles were included in this review.

Conclusion: titanium remains the optimum implant material. The optimum surface modification is SLA for titanium and TiO2 plasma spray for carbon fibre-reinforced polyetheretherketone-hydroxyapatite. Further long-term animal trials directly comparing titanium and PEEK as well as further research into carbon fibre-reinforced polyetheretherketone-hydroxyapatite would be very recommendable.

Key words: *Titanium, PEEK, osseointegration, surface modification.*

Introduction

Implants are the gold standard treatment; they have great success rates and long-term longevity. Titanium has been the material of choice in implants since the last 60 years. Dentistry is forever seeking to improve upon its previous advances in order to optimise outcome. Concerns with the stiffness of titanium in relation to bone has given way to research for new materials as potential replacements, PEEK being a potential competitor (1)

Osseointegration can be comprehensively defined as “the process resulting in direct structural and functional connection between ordered, living bone and the surface of a (load bearing) implant” (2). To gain optimal anchorage and mechanical stability, direct bone to implant contact is required (BIC), providing the basis for desired dental implant functioning (2)

Titanium has a wide range of biomedical applications including dental implants, joints, screws, bone plates and cardiovascular devices. This is thanks to its great biocompatibility; it is relatively inert and corrosion resistance. These accolades contribute to its high osseointegration success (13,14). Its inertness is a result of the metals passivity. Passivation is defined as the process of transforming a chemically active surface of a metal to a less active surface (5). Titanium will react with oxygen to form tio2 readily in air. It can also reform this oxide protective layer in vivo; it reduces corrosion rate and the oxidising layer can be maintained over long term fatigue also. Over long periods of time, this oxide layer can theoretically be penetrated when factoring in acidic conditions, such as inflammatory bouts found at the mechanical wear sites (6).

Titanium surface modifications are split into mechanical and chemical methods. Mechanical methods include plasma spray and sand grit blasting method. Chemical methods include etching, anodization, and antibacterial coating(3). Anodization implements acid etching in combination with electrical impulses to partially dissolve the oxide layer and substitute it with ions derived from the acids. The antibacterial coatings reduce inflammation responses experienced during the healing phase. This creates a better environment for bone to implant contact due reduced connective tissue volume (3).

There are concerns of titanium's aesthetic outcome, for example, in cases of patients with thin biotype mucosa, a grey colour can become visible (7). Even in cases of peri-implant resorption or gingival recession, the neck would reveal grey hue of titanium. Resorption can arise as a result of titanium's high modulus of elasticity compared to bone. It is more than 7x higher (110 gpa compared to 15 of cortical bone)(7). As mentioned earlier the disparity can give rise to stress shielding. It is especially present in the junction between the prosthesis and implant body. This can develop in further resorption and subsequent implant failure. It also gives scattered images during radiographic analysis, which makes image reading more difficult for the dentist. (7–9).

PEEK was developed in 1978 by a group of English scientists(9). It is a high-performance polymer, being a member of PAEK (polyarylether ketone) polymer family. It is a semi crystalline polycyclic linear aromatic structure(10). Essentially it falls under the category of a plastic.(11) Due to Its excellent biocompatibility, there has been no reports of cytotoxicity or adverse reactions. It has been used in the field of orthopaedic devices and traumatology to replace hard tissues. In dentistry it can be applied in removable prosthesis (framework and artificial teeth), fixed bridges and crowns and implants (20). It has thermal stability above 300c high mechanical resistance, high physical resistance, and water resistance (18,19,21).

PEEK has become an increasingly popular researched implant material alternative. It solves the issues presented by titanium. It can meet aesthetic requirements; its colour is closer to that of bone. Its elastic modulus is closer to that of cortical bone also (pure form 3-4 gpa) and it can be reinforced with to carbon fibre or glass (12 gpa and 18 gpa respectively). Therefore being more stress protective. (7,13)

Material and Methods

- Inclusion criteria

The PRISMA guidelines has been followed to prepare this systematic review(22).
(P) Population - Dental patients treated with endosseous implants
(I) Intervention - PEEK materials as the implant body
(C)Comparison - Titanium as the implant body material
(O)Outcome - Increased osseointegration according to parameters (BV/TV, BIC or BA)

In addition, the studies had to meet the following requirement:

(Type of article) Published within the last 10 years (up to 2012) and in English

- Exclusion criteria
    - in-vitro studies not including in vivo experiment, studies without BV/TV, BIC, or BA variables

- Search strategy

A comprehensive literature search was conducted on the following databases: MEDLINE complete (through the UEV interface) and SCOPUS (through the UEV interface) on 05/03/22. Boolean operators “AND”, “OR” and “NOT” were utilized to compose the search algorithm, the following sequence shows the order in which the keywords were composed:(“peek dental implants” AND “polyether ether ketone” AND “surface modification” OR “CFR PEEK dental implants” OR “GFR PEEK dental implants” OR “titanium dental implants” AND “comparison” AND “surface modifications” AND “osseointegration” NOT “zirconia”)

- Selection process

Firstly, the duplicate articles were removed. Following this, the remaining titles and abstracts were revised to satisfy pertinence and only articles referring to the implant body were selected (not to the implant crown or abutment). Thereafter, the eligibility criteria were applied through full-text assessment.

- Data extraction

Included studies were summarise into two tables: general characteristics of included studies and results of included studies.

- Quality Evaluation

Each study included in this systematic review was screened using the CASPe (critical appraisal skills program) checklist(15). It serves as checklist guide for each article being comprised of 12 specific criteria. The studies are filtered through these criteria being categorised into “yes”, “no” or “cannot tell”. Lastly, each study receives a score unto 12 to provide a quantitative value of their methodological quality.

Results

101 articles were identified (SCOPUS 21, MEDLINE complete, 2 duplicates were removed, 99 articles were considered for title and abstract evaluation. At the end of this evaluation step, 13 articles were identified for full text review (293 articles excluded). Of the 13 articles selected, 3 articles were excluded. 10 articles were included in this systematic review. The process of study selection is represented as a flowchart in figure 1.

- Evaluation of bias

Each study included in this systematic review was screened using the CASPe (critical appraisal skills program) checklist(15). It serves as checklist guide for each article being comprised of 12 specific criteria. The studies are filtered through these criteria being categorised into “yes”, “no” or “cannot tell”. Lastly, each study receives a score unto 12 to provide a quantitative value of their methodological quality. It is shown in table 1

- Synthesis of results

The characteristics and results of the included studies are presented in Tables III and IV in the annex. Table II represents General characteristics followed according to the titles: country, type of study, sample size, animal studied, mean age, study groups (control and test), time until sacrifice, study variables and risk of bias. Table III represents results of included studies followed according to the titles: author and year, implant material, surface modification control, surface modification control, implant design, BIC, BV/TV, Bone area and statistical significance.

All 10 studies are randomized control trials, 6 are surface modifications for

titanium implants, 4 are surface modifications for PEEK materials. Of the titanium surface modifications 4 studies test sand blasting methods and 2 studies test oxidation methods. Of the 4 PEEK studies, 2 studies utilise antibiotic coating, one study utilises growth peptide and the other uses titanium plasma spray on a hydroxyapatite carbon fibre PEEK.

Discussion

Titanium is the gold standard currently in dental implants since the last 60 years. It has excellent osseointegration due to its passivity, readily oxidising to create a TiO_2 surface layer. This oxide layer promotes osseointegration and maintains the surface inertia(1). Osseointegration is defined as “the process resulting in direct structural and functional connection between ordered, living bone and the surface of a (load bearing) implant” and is paramount for implant success(2). Methods of preparing titanium surfaces include mechanical methods such as sand blasting and chemical methods such as micro arc oxidation(3). Titanium’s disadvantages are related to its colour, radiopacity, and long-term apical bone resorption resultant of stress shielding(7–9) . Peek on the other hand has excellent structural properties. It has similar elastic modulus to bone avoiding stress shielding. It is not radiopaque, nor does it produce any scattering effect in the radiograph(7,13). The colour can match bone creating better aesthetics, especially in the anterior sector. However, due to PEEKs highly inert surface and lack of passivity, the osseointegration is poor in unmodified surfaces. It requires surface modification to promote osseointegration(9). If this can be achieved, along with is established structural benefits. It can be a competitive material alternative to titanium implants.

Titanium surface modifications

Wulin He et al.(17) compared the osseointegration of Micro arc oxidation (MAO) and large grit sand blasting and acid etch (SLA) as two the control groups achieving 60% and 78% BV/TV respectively. Large grit sand blasting combined with acid etch (SL-MAO) achieved 68% BV/TV in the test group. Eugenio Velasco-Ortega et al. (16) also investigated a sand blasting technique (SA) as the control group reporting less the surface roughness from the SEM

measurements, 1.74um (SA) versus 2.13um (SLA). Similarly, shown in both the BIC and BV/TV results, the sand blasting method was superior to the oxidised test group in Eugenio Velasco-Ortega et al. (16)(17)The oxidised test group (OS) had the lowest roughness at 1.37um surface roughness. This suggests roughness is has a positive correlation to BV/TV%.

However, the results were not statistically significant between OS and SA neither in BIC results nor in the BV/TV results in the study conducted by Eugenio Velasco-Ortega et al(16). There were different implant designs for the control group (SA) and the oxidised test group (OS), this could also affect the statistical significance of the results.

Young-Sun Hong et al.(18)and Won-Tak Cho et al.(19)both conducted experiments with modified SLA surface modifications on titanium. Young-Sun Hong et al.(18) demonstrated similar outcomes of modified SLA being superior to its control group however the statistical differences were not significant. This perhaps could be due to the implant designs being different, the healing period was only one week or the lack of test subjects. One week is not sufficient to allow for osseointegration (see figure 2). To conclude, better results were attained in Wulin He et al. (17) experiments with unmodified SLA (Bone area 85%) compared to GR, GA, and mod SLA (Bone area 52%, 43.8%, 42.6% respectively)

Won-Tak Cho et al (19)and Wulin He et al.(17)had similar sample sizes and the same animal test subjects. The BIC% results (GR 60.2% (19)BIC SLA 60% BIC (17)) are very similar but the bone area % is higher in Wulin He et al.(17).

Ping-Jen Hou et al.(20) achieved the highest BIC value recorded amongst the titanium BIC results 88.1% at 12 weeks. This study only measured BIC% as the only indicator for in vivo osseointegration. The control group was unmodified titanium (M-Ti). The unmodified titanium also achieved very high BIC values, the second highest in all the titanium BIC percentages. This reduces the credibility of Ping-Jen Hou et al. (20), in the study conducted by Guanglong Li et al.(21) we can see the untreated titanium was credited with a BIC percentage of 10.4% almost 7x lower than untreated titanium result of Ping-Jen Hou et al.(20). Ping-Jen Hou et al. (20) was the only experiment to use mini pigs as the test subjects

perhaps contributory to its high osseointegration. Furthermore, there is no bone area nor BV/TV to compare against other studies therefor we will isolating the result as an potential outlier.

The most accurate and reliable study is Wulin He et al.(17), it combines SLA MAO and SL-MAO into one article under the same conditions. It shows statistical significance between each dependant variable and includes all three BIC, BV/TV and BA. The healing time given to the subject was 12 weeks, this complies best with osseointegration opposed to 8 weeks or less.

PEEK surface modifications

In the PEEK studies, BV/TV was the only osseointegration dependant variable, the control group for three out of four studies was bare PEEK or nature PEEK, also known as untreated peek. The BV/TV values indicate clearly that it is not comparable in its raw form against titanium (Zhiqiang Xue et al.(22) 8.5% BV/TV, Maihemuti Yakafu et al.(23) 11% at four weeks BV/TV, Xiao Xu et al.(24) 9% BV/TV. Anxiu Xu et al.(25) control group is a fourth is a structurally enhanced modified PEEK. More specifically, carbon fibre-reinforced polyetheretherketone-hydroxy apatite (PEEK/n-HA/CF). unmodified PEEK/n-HA/CF achieved a BV/TV percentage of 46%, significantly higher than bare PEEK.

Maihemuti Yakafu et al.(23) osteogenic growth peptide to PEEK surface to create PEEK- OGP. The BV/TV values for PEEK OGP were 27% and 28% at 2 weeks and 4 weeks respectively. It has shown similar results to dex/mino PEEK (24), demonstrating its effectiveness over bare unmodified PEEK. Nonetheless, the BV/TV percentages were not as high as titanium SLA(17). Although, the healing period was only 2 and 4 weeks after implantation. Perhaps the BV/TV% could be higher with a longer healing period.

According to Anxiu Xu et al. (25), a healing period of 4 weeks, p-m-PEEK/n-HA/CF showed great potential achieving a BV/TV value of 58% and being statistically significant to all three groups. Differences between unmodified Titanium, PEEK/n-HA/CF and p-PEEK/n-HA/CF were not statistically significant. The experiment was conducted well, the control group was especially pertinent since the PEEK material could be compared directly against unmodified titanium.

Anxiu Xu et al. (25) achieved the highest BV/TV percentage compared to the four PEEK materials studied. Macroscopically it has been enhanced, the elastic modulus is closer to human bone when PEEK is combined with carbon fibre. This technique amalgamates both superior qualities of PEEK and titanium- it provides excellent elastic modulus and the TiO_2 spray forms an oxidised layer bringing adhesion and high rugosity (3.19 um)(25). When comparing BV/TV% of p-m-PEEK/n-HA/CF to BV/TV% of SLA titanium there is a difference of 20% (17), however p-m-PEEK/n-HA/CF had a healing period of 4 weeks and SLA titanium had a healing period of 12 weeks. We have seen in study conducted by Ping-Jen Hou et al.(20) that the difference between 8 and 12 weeks in BIC% reveals statistically significant results. If the p-m-PEEK/n-HA/CF study was repeated with longer healing period (12 weeks) the BVTV% is likely to be higher, thus making p-m-PEEK/n-HA/CF a potential competitor to the SLA titanium in the Wulin He et al.(17)study.

Limitations

The studies collected lacked universal uniformity, it was not possible to find different studies following the exact same surgical technique and methodology. They had different implant designs between the control group and the test group. Healing time is another variable that greatly varied between studies. Only two studies had more than 10 test subjects, this negatively affects the repeatability of the experiments. Implant location is another modifiable factor not kept constant throughout the experiments, only two studies implanted into the mandibular bone (being the most appropriate location). Lastly, only one of the ten articles measured all three dependant variables (BV/TV, BIC, BA) (Wulin He et al.(17). The PEEK studies only provided BV/TV as the osseointegration dependant variable. This made it especially difficult to provide repeatability in this systematic review since there is only one variable to compare against. Among the titanium articles, BA and BIC variables showed positive correlation comparing to BV/TV, making the BV/TV% a reliable marker for osseointegration.

Implications

Further studies need to compare PEEK/n-HA/CF to titanium SLA under the same conditions to extract a definitive conclusion including all three osseointegration variables. Since it is a new material more research must be conducted until it can be used in patients, it has shown potential for high osseointegration success when compared to titanium.

Future investigations

Long-term animal studies directly comparing the osseointegration of PEEK and Titanium would be incredibly useful. This would ensure both materials are under the same conditions, focusing on its in vivo ability including all three variables (BV/TV, BIC, and BA).

Conclusion

Within the limitations of this review, we can conclude that: titanium remains the optimum implant material versus PEEK. TiO_2 plasma treatment was the best performing surface modification for PEEK, specifically carbon fibre-reinforced polyetheretherketone-hydroxyapatite (PEEK/n-HA/CF) . SLA titanium is the best performing surface modification for titanium. Further long-term animal trials directly comparing titanium and PEEK as well as further research into carbon fibre-reinforced polyetheretherketone-hydroxyapatite would be very recommendable.

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Annex

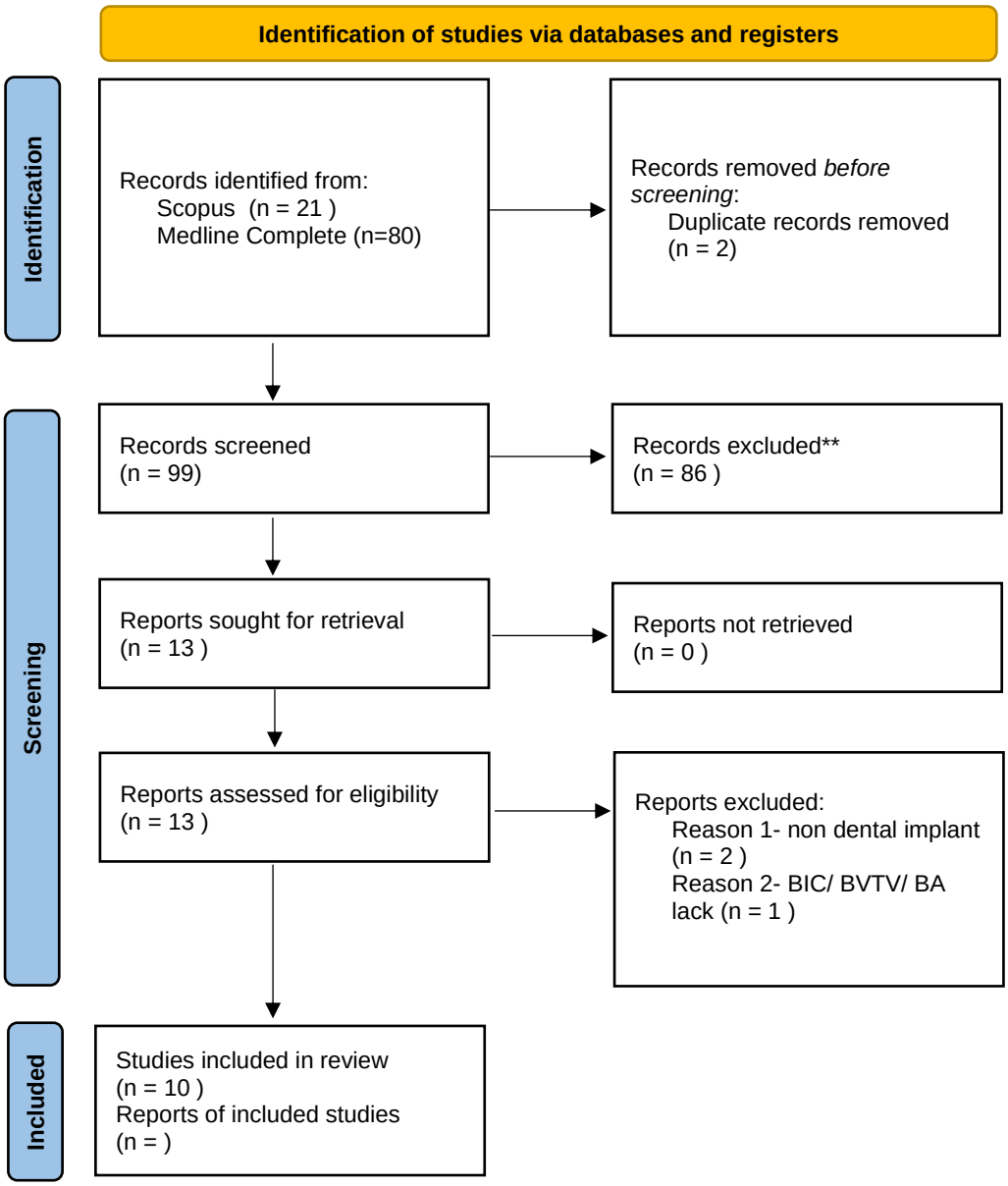

Figure 1: Flowchart of the selection process of articles for the systematic review.

Table I: CASPe checklist for randomised control trials

	Wulin He 2019	Young-Sun Hong 2014	Eugenio Velasco-Ortega 2019	Won-Tak Cho 2021	Ping-Jen Hou et al. 2017	Guanglong Li 2016	**Zhiquang Xue 2020**	Maihemuti Yakufu 2020	Xiao Xu 2018	Anxiu Xu 2014
1. Did the study address a clearly focused research question?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was the assignment of participants to interventions randomised?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Were all participants who entered the study accounted for at its conclusion?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. 4. Were the participants 'blind' to intervention they were given?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Were the investigators 'blind' to the intervention they were giving to participants? Were the people assessing/analysing outcome/s 'blinded'?										
5. Were the study groups similar at the start of the randomised controlled trial?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6. Apart from the experimental intervention, did each study group receive the same level of care?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Were the effects of intervention reported comprehensively?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

8. Was the precision of the estimate of the intervention or treatment effect reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9. Do the benefits of the experimental intervention outweigh the harms and costs?	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
10. Can the results be applied to your local population/in your context?	Y	N	N	Y	Y	Y	Y	Y	Y	Y
11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	Y	N	N	Y	Y	Y	Y	Y	Y	Y

Table II General characteristics of included studies

Author/ Year	Country	Type of study	Sample			Study groups		Time until animal sacrifice (weeks)	Study variables	Risk of bias
			Sample size	Animal studied	Mean age (months)	Control	Test			
Wulin He et al. 2019 (17)	China	Randomized Controlled Clinical Trial	4	Beagle dog	12	16	8	**12**	BIC (mean %) BV/TV (mean mm) BA(mean %)	LOW
Young-Sun Hong 2014 (18)	Korea	Randomized Controlled Clinical Trial	3	Rabbit	18	3	3	1	BIC (mean %) BA (mean %)	MEDIUM
Eugenio Velasco-Ortega 2019 (16)	Spain	Randomized Controlled Clinical Trial	6	Rabbit	6.5	12	12	12	BIC(mean %) BV/TV (**%**)	LOW
Won-Tak Cho 2021 (19)	Korea	Randomized Controlled Clinical Trial	6	Beagle dog	36	12	24	8	BIC(mean %) NBA	LOW
Ping-Jen Hou et al. 2017 (20)	Taiwan	Randomized Controlled Clinical Trial	6	Minipig	12	6	6	8 and 12	BIC (mean %)	LOW

Guanglong Li, 2016 (21)	China	Randomized Controlled Clinical Trial	12	Beagle dog	12	12	24	6	BIC % NBA	LOW
Zhiqiang Xue al.2020 (22)	China	Randomized Controlled Clinical Trial	15	Rat	6	15	15	6	BV TV %	LOW
Maihemuti Yakufu 2020 (23)	China	Randomized Controlled Clinical Trial	10	Rat	3	10	10	2 and 4	BV TV %	LOW
Xiao Xu 2018 (24)	China	Randomized Controlled Clinical Trial	3	Beagle dog	18 months	8	8	8	BV/TV %	LOW
Anxiu Xu 2014 (25)	China	Randomized Controlled Clinical Trial	6	Beagle dog	18 months	6	18	4	BV/TV **%**	LOW

Table III – results of included studies

Author and year	Implant material	Surface modification control	Surface modification test	Implant design	BIC (%)	BV/TV (%)	Bone area (%)	Statistical significance
Wulin He et al. 2019 (17)	Titanium	large-grit sandblasting and acid etching (SLA) micro arc oxidation (MAO)	large-grit sandblasting combined with micro-arc oxidation (SL-MAO)	Ø 3x10mm Rod shaped Femur	MAO = **43** SL-MAO =52 SLA = **60**	MAO= 57 SL-MAO= 68 SLA = 78	MAO = 70 SL-MAO = 80 SLA= 85	Statistical significance between SL-MAO and SLA/MAO in both BIC and BA respectively
Young-Sun Hong 2014 (18)	Titanium	F-mod	modSLA	F-mod Ø3.5mmx11mm modSLA Ø3.3mmx10mm Tibia	F-mod = 34.4 modSLA = 36.9	-	F-mod = 34.8 modSLA = 42.6	No statistical significance
Eugenio Velasco-Ortega 2019 **(16)**	Titanium	Acid etched with sand blasting treatment (SA)	Oxidised implant surface (OS)	SA = Ø 4x10mm OS = Ø 4.1x	SA = 53.49 OS = 50.94	SA Cervical 41 Medial 30 apical 42	-	No statistical significance

				10 mm Femoral condyle		OS Cervical 39 medial 20 apical 48		
Won-Tak Cho 2021 (19)	Titaniu m	Non-treated sandblasted acid etched (SLA)	SLA with Crosslinking collagen type I gamma rays (GR) SLA with Crosslinking collagen type I glutaraldehyde (GA)	Ø 4x8 mm Mandibular bone	SLA = 47.3 GA = 54.6 GR = 60.2	-	SLA = 38.2 GA = 43.8 GR = 52.3	No statistical significance in bone area BIC was significantly greater in the GR group than in the SLA group
Ping-Jen Hou et al. 2017 (20)	Titaniu m	M-Ti **Untreated titanium**	MST-Ti optimal micro-arc oxidation surface-treated titanium	Ø 3.5x8mm Mandible bone	Week 8 M-Ti = 70.0 MST-Ti = 76.9 Week 12 M-Ti = 71.8 MST-Ti = 88.1	-	-	Statistically significant at 8 weeks and 12 weeks
Guangl ong Li,	Titaniu m	Micro arc oxidation MAO	Micro arc oxidation reduced. In	Ø 3x10m	MAO = 55.9	-	MAO = 20.6	BIC and NBA

2016 (21)		Ti unmodified	alkali solution MAO-AK	m rod shaped Left femur	MAO-AK = 32.8 Ti unmodified = 10.4		MAO-AK = 37.0 **Ti Unmodified = 13.3**	statistically significant for MAO-AK group compared to MAO
Zhiquang Xue et al. 2020 (22)	PEEK	Bare peek	PEEK/CaP-GS*3 PEEK/CaP-GS*6 PEEK/CaP-GS*9	Ø 2x5 mm Femur	-	Natural PEEK = 8.5 PEEK/CaP-GS*3 = 11 PEEK/CaP-GS*6 = 15 PEEK/CaP-GS*9 = 15.5	-	Compared with natural PEEK implants, PEEK/CaP-GS groups have significantly higher BV/TV
Maihemuti Yakufu 2020 (23)	PEEK	Bare PEEK	Osteogenic growth peptide PEEK (OGP)	Ø2x6mm Tibia	-	2 weeks Peek = 7 Peek OGP = 27	-	Results between peek and peek OGP are statistically significant Results

						4 weeks Peek = 11 Peek OGP = 28		between PEEK OGP at two weeks and four weeks are also statistically significant.
Xiao Xu 2018 (24)	PEEK	Bare peek	Dexamethasone plus minocycline-loaded liposomes with polydopamine coated PEEK (dex/mino)	Ø4x7mm femur	-	PEEK = 9 PEEK DEXMINO = 27	-	Difference is statistically significant
Anxiu Xu 2014 (25)	PEEK	Pure titanium	carbon fiber-reinforced polyetherketone nanohydroxyapatite biocomposite(PEEK/n-HA/CF) plasma-modified micro-structured (p-m-PEEK/n-HA/CF) plasma-modified smooth (p-PEEK/n-HA/CF)	Ø 4x7 mm 3rd 4th premolar	-	Ti = 47.5 PEEK/n-HA/CF = 46 p-PEEK/n-HA/CF = 49 p-m-PEEK/n-HA/CF = 58	-	BV/TV is significantly highest in p-m-PEEK/n-HA/CF