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FACULDADE DE MEDICINA DENTÁRIA
VISEU

OSSEOINTEGRATION OF ZIRCONIA AND TITANIUM IMPLANTS: SYSTEMATIC REVIEW

Dissertação apresentada à Universidade Católica Portuguesa
para obtenção do grau de Mestre em Medicina Dentária

Por:
Maria João da Silva Remísio

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Orientador: Prof. Doutor Tiago Borges
Coorientador: Prof. Doutor Gustavo Fernandes

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“I am still learning.”
- Michelangelo

Dedico este trabalho aos meus pais,
meus maiores e melhores orientadores na vida.

AGRADECIMENTOS

Prof. Doutor Gustavo Fernandes, obrigada pela oportunidade de trabalhar consigo neste projeto, pelas suas orientações e conselhos que tornaram possível a concretização deste trabalho e majoraram a minha competência científica e profissional.

Prof. Doutor Tiago Borges, pela sua disponibilidade e orientação na realização deste projeto.

Aos meus amigos da faculdade, pelo companheirismo nesta etapa da nossa vida profissional e pessoal.

A todos os professores, pelo compartilhamento de conhecimento, que possibilitou a minha formação profissional.

À Universidade Católica Portuguesa, pela oportunidade de realizar este projeto e concretizar a minha formação profissional.

ABSTRACT

Introduction: Titanium implants are the gold standard, but due to problems with aesthetic and structural components, there has been an increase in research for zirconia implants. They have ivory color, good biomechanical characteristics, and a satisfactory survival rate. Thus, this study's goal was to systematically verify the literature to compare the osseointegration levels between titanium and zirconia dental implants, shown through histological analysis.

Material and Methods: This review was conducted following the PRISMA guidelines and was registered in PROSPERO. Electronic and manual searches were carried out through PubMed/Medline, PMC, and Embase databases, with a platform-specific search strategy combining controlled terms (MeSH and Emtree) and text words. The selection of articles was carried out by two independent investigators and Cohen's kappa coefficient was used to assess the agreement, which was then evaluated using the defined inclusion and exclusion criteria.

Results: From the initial 271 abstracts screened, 17 articles were included for full-text reading. All of them were preclinical in vivo studies that compared the osseointegration level between zirconia and titanium implants. A total of 370 titanium implants (Ti) and 537 zirconia implants (Zr) were evaluated. The percentual average of osseointegration for Zr was 55.51% (min. 17.6% and max. 89.09%), whereas Ti was 58.50% (min. 23,2% and max. 87.85%). There was no statistical difference between studies at 2 months of histomorphometry ($p = 0.672$). While for the studies analyzed at 1 month and 3 months, statistically significant data of $p < 0.001$ were found for both.

Conclusion: Zirconia implants have presented a similar level of osseointegration compared to titanium implants. Therefore, based on results on osseointegration it was conceivable to conclude that Zr implants are a viable choice for oral rehabilitation. Nonetheless, because these findings are based on preclinical research, all data must be thoroughly examined, and clinical trials evaluating osseointegration of Ti and Zr implants are required.

Keywords: Dental implants, Osseointegration, Systematic Review.

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LIST OF ABBREVIATIONS AND ACRONYMS

cpTi- Commercially pure titanium

GPa- Gigapascal

BIC- Bone-to-implant contact

Al_2O_3- Aluminum oxide

Y-TZP- Yttria-stabilized tetragonal zirconia polycrystal

ZrO_2 - Zirconium dioxide

Y_2O_3- Yttrium(III) oxide

MPa- Megapascal

PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PICO- Population, Intervention, Comparison, and Outcome

Zr - Zirconium

TZP- Tetragonal Zirconia Polycrystal

ATZ - Alumina Toughened Zirconia

SEM- Scanning electron microscope

HA- Hydroxyapatite

1. INTRODUCTION

1. Introduction

Implant dentistry has progressed from an experimental procedure to a highly predictable treatment option for replacing lost teeth with implant-supported prostheses on fully and partially edentulous patients.[1]

The fundamental goals of implant therapy are to obtain satisfactory treatment results in terms of function, esthetic, and phonetics with high predictability and long-term stability, and minimal risk of complications. It is also essential to carry as few surgical interventions as possible, as little pain and morbidity as possible during healing, short healing periods, and a short overall treatment time.[1]

The success of implant placement relies upon the patients' diagnosis regarding their periodontal condition, available bone, occlusion, and general health. As a result, an appropriate treatment option and selection of the implant's biomaterial for each clinical case can be made.[2,3]

Modern implantology standard protocols were first developed by Brånemark et al[4], with the introduction of endosseous, osseointegrated implants. These implants were made of rough-surfaced commercially pure titanium (cpTi).[5]

Currently, the most often used dental implant materials are commercially pure titanium (cpTi) and zirconium dioxide (zirconia). Because of its excellent biocompatibility and mechanical qualities, cpTi is the most used dental implant. However, because of titanium's grey color, it may cause aesthetic issues when used. As a result, zirconia implants are a viable option for aesthetic-driven rehabilitative procedures. Indeed, zirconia has less plaque accumulation in addition to having an ivory color, resulting in better soft tissue management and a more pleasing appearance.[3]

There are various factors of an implant that influence its lifetime and success. Implant materials should have a modulus of elasticity equivalent to bone (18 GPa), high tensile, compressive, and shear strength, high yield and fatigue strength, at least 8% ductility, and increased hardness and toughness, among other bulk properties.[3]

Another critical factor in implant biomaterials is the bone-implant interface. On one hand, adequate bone mineralization ensures high-quality bone-to-implant contact (BIC) and the long-term biomechanical stability of implants. On the other hand, a risk factor for implant failure is a decline in bone quality in an impaired condition.[6]

Conclusively, the interaction between bone and biomaterial determines the implant's longevity, and osseointegration is required for successful therapy. Therefore, efforts should be made to discover improved means of enhancing implant osseointegration. In fact, roughness, chemical composition, and mechanical factors on the surface of dental implants can all contribute to early osseointegration. As a result, preclinical research's main focus has been to improve osseointegration through advancements in dental implant design, surface characterization, and implant insertion procedures.[6,7]

1.1. Osseointegration

Osseointegration is defined as the establishment of contact between normal remodeled bone and an implant without the interposition of nonbone tissue, resulting in a sustained transfer and distribution of load from the implant to the bone tissue. In clinical terms, osseointegration refers to an implant's stability and functional ankylosis in a bone.[7]

Biologically, osseointegration has been proposed as an immune-driven process that results in new bone production. According to research, implants have a tolerogenic balance with peri-implant tissues, resulting in a foreign body equilibrium response. As a result, the bone-implant contact is thought to be regulated by the immune response, using the same processes as tissue healing and regeneration. To summarize, the immune system first recognizes the implant as a foreign body and then forms bone around it as a defense reaction to shield the implant from the surrounding tissues.[8–10]

Furthermore, research has shown that the long-term maintenance of foreign body equilibrium is the key to the longevity of implant osseointegration. In fact, a balance between antimicrobial and proinflammatory M1-macrophages and anti-inflammatory and pro-regenerative M2-macrophages correlates with wound healing, regeneration, and osseointegration.[8,11]

Moreover, the dynamic process of osseointegration happens during the implant's primary stability to secondary stability. Secondary stability is built up beginning with the first apposition of new bone onto the implant surface.[12]

Osseointegration rates of implants can be influenced by clinical and inherited patient factors such as periodontal infections or smoking habits. As a result, creating implant biomaterials that osseointegrate as well as possible is critical. In this regard, osteoimmunomodulation is a promising strategy for enhancing implant osseointegration.(8)

Diverse implant materials, designs, and surface properties (topographical, chemical, mechanical, and physical) have different osseointegration implications. Indeed, studies show that rough implant surfaces promote osseointegration more than smooth surfaces and that hydrophilic surfaces promote osseointegration.(13–15)

Regarding evaluating osseointegration, histomorphometry is the gold standard for assessing how much bone is in contact with an implant surface. In these analyses, bone-to-implant contact (BIC) is measured and quantified as the percentage of the implant surface covered by bone.(12)

1.2. Titanium Implants

Titanium implants have been regarded as the gold standard biomaterial for decades due to their biomechanical properties that enable excellent strength, biocompatibility, and osseointegration.(16,17) As a result, titanium implants have a high survival rate. According to research, a five-year observation period yielded a survival rate of 94.7 % to 99.4 %, and a ten-year observation period yielded a survival rate of 96.4 %.(16)

Titanium implants, on the other hand, have a few drawbacks. Tribocorrosion occurs when free metallic ions are released from the titanium implant surface. T-cells may mediate type IV hypersensitivity and inflammatory reactions due to this process. Furthermore, titanium corrosion may affect implant osseointegration by directly activating osteoclasts and osteoblasts or stimulating inflammatory cytokine secretion. To summarize, titanium can cause proinflammatory and hypersensitivity/allergic effects, which can lead to contact dermatitis, pain, swelling, delayed healing, and, in the end, failure of the implant's therapy.(16–19)

Furthermore, titanium implants used in esthetic areas do not always produce good esthetic results due to discoloration of peri-implant soft tissue, which results in a greyish shade and mucosal recession.[16,20]

Regarding osseointegration, research has shown that without surface treatment, titanium has greater osseointegration than zirconia; following surface treatment, both materials have equivalent osseointegration.[21]

1.3. Zirconia Implants

As a result, there has been an increase in research into new implant materials, particularly ceramic materials. Ceramics used in implants include densely sintered alumina (Al_2O_3) and yttria-stabilized tetragonal zirconia polycrystal ceramic (Y-TZP). In terms of implant body's, however, evidence suggests that Y-TZP outperforms other ceramics.[18,22]

Y-TZP is a bioinert, non-resorbable biomaterial composed of ZrO_2 and Y_2O_3 molecules. Zirconia implants have a low modulus of elasticity, resulting in high strength levels. This material also has a low modulus of thermal conductivity, a high flexural strength (900–1.200 MPa), a high radiopacity, excellent corrosion and wear resistance, a low affinity to plaque, high biocompatibility, and research has shown they have good osseointegration, but there is still no consensus in these results, thus further research on the matter is required.[18,22–24]

Furthermore, due to their surface, zirconia implants have demonstrated better clinical outcomes in soft tissue integration, resulting in a lower amount of pathogen adhesion. Studies have shown that zirconia and titanium have similar clinical outcomes in oral health conditions, but zirconia implants perform better under experimental mucositis conditions, particularly plaque and bleeding scores. Furthermore, zirconia implants can transmit light and have an ivory coloration, allowing for better esthetic results with mucosa coloration on anteriorly located implants.[18,20,22,24,25]

Finally, the mean survival rate of one-piece zirconia implants was greater than 98%, with low marginal bone loss in 3- and 5-year follow-up studies. According to research, micro rough zirconia implants have a similar osseointegration capacity to micro rough titanium implants under unloaded and loaded settings. On the other hand, titanium exhibited a faster initial osseointegration process than zirconia.[26,27]

Despite this, zirconia implants have some disadvantages, such as low-temperature degradation, reducing the implant's strength, toughness, and density.(18,22,23)

In addition, research has shown that zirconia requires surface modification to have a similar osseointegration rate to titanium implants. Moreover, with surface treatment, the removal torque value of zirconia implants was enhanced, but it was not greater than that of titanium implants. As a result, zirconia implants are still not suggested due to a lack of scientific proof for their clinical application.(21)

Conclusively, while zirconia implants are a promising treatment option due to their excellent biocompatibility characteristics and satisfactory survival rates, more research on osseointegration and mechanical stability is required.

1.4. Objectives

Thus, to obtain a systematization of the current knowledge on osseointegration of titanium and zirconia implants, we carried out a systematic review of the literature, as this is the type of study with the most recent studies and significant scientific evidence.

As a result, the main goal of this systematic review is to evaluate and compare the osseointegration rates, through histological analysis, of zirconia *versus* titanium implants.

2. MATERIALS AND METHODS

2. Materials and Methods

2.1. Study Type

To achieve the goal of this study, a systematic review was developed. Systematic reviews use scientific strategies to minimize bias via explicit and systematic methods. Therefore, it is possible to execute an extensive bibliographic search and identify, select, and critically analyze published scientific studies of the topic of interest.[28–30]

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed for this systematic review. The focused question was determined using the Population, Intervention, Comparison, and Outcome (PICO) strategy.[28,29,31]

Moreover, this study was registered in the PROSPERO platform (Annex 1).

2.2. Focused Question

Do subjects (P) rehabilitated with zirconia implants (I), compared to titanium implants (C), exhibit different osseointegration outcomes at histological levels (O)?

Table 1 - Formulation of the PICO research question.

Patient/Population	Subject that received dental implant
Intervention/Indicator	Zirconia implants
Compare/Control	Titanium implants
Outcome	Histological analysis, Survival rate, Osseointegration, Bone loss

2.3. Information Sources and Search Strategy

An extensive electronic search was conducted through PubMed/Medline®, PubMed Central® (PMC), and Embase® databases with a platform-specific search strategy combining controlled terms (MeSH and Emtree) and text words, detailed in Table 2. An additional manual search was performed on the references of included articles to identify relevant publications.

Only articles published in the English-language dental literature from February 2012 until and, including, February 2022 were included. Two reviewers (M.R. and G.F.) independently performed the electronic and manual search.

The publications obtained from the search through all mentioned databases were imported into a reference management software (EndNote X9/ Thomson Reuters, Philadelphia, U.S.A.) and subsequently screened.

2.4. Inclusion Criteria

This systematic review was based on a clinical trial, prospective (PS) and retrospective (RS) clinical studies, case series, and pre-clinical studies, which developed a histologic analysis of the osseointegration of titanium and/or zirconia implants.

The additional inclusion criteria for study selection were:

- English-language dental literature, from February 2012 until February 2022;
- Titanium and/or Zirconia dental implants used;
- Detailed information on the implant;
- Reported details regarding osseointegration;
- Only the publication with the most extended follow-up was included in the case of multiple studies involving the same patient cohort (population).

Table 2- Search Strategy Terms and Equations		
	PubMed/Medline® and PubMed Central® (PMC)	Embase®
#1	**P – Patients or animals that received dental implants**	
	((“Dental Implants" [MeSH Terms]) OR (“Dental Implants, Single-Tooth" [MeSH Terms]) OR (Dental Implant* [Supplementary Concept]))	(‘tooth implantation’/exp OR ‘tooth implant’/exp OR ‘dental implant’/exp)
#2	**I – Zirconia dental implants**	
	((“Zirconium” [MeSH Terms]) OR (Zirconium Oxide [Supplementary Concept]) OR (Zirconia [Supplementary Concept]) OR (Yttria Stabilized Tetragonal Zirconia [Supplementary Concept]) OR (“Ceramics” [MeSH Terms]))	(‘zirconium oxide’/exp OR ‘zirconium’/exp OR ‘ceramics’/exp OR ‘yttria stabilized tetragonal zirconia’/exp)
#3	**C – Titanium dental implants**	
	((“Titanium" [MeSH Terms]) OR (“Rehabilitation" [MeSH Terms]))	(‘titanium’/exp OR ‘rehabilitation’/exp)
#4	**O – Histological findings, survival rate and complication outcomes**	
	((“Histology” [MeSH Terms]) OR (“Histological*”) OR (“Osseointegration”) OR (“Survival rate”) OR (“Surface”) OR (“Bone loss”))	(‘histology’/exp OR ‘osseointegration’ OR ‘survival rate’/exp OR ‘Surface’/exp OR ‘bone loss’/exp)
Search Combination	(#1 AND #2 AND #3 and #4)	
Filters	English, Time (last 10 years)	

2.5. Exclusion Criteria

Clinical studies that did not meet the entire inclusion criteria were excluded. Reports based on questionnaires, interviews, case report, in vitro studies were rejected as well as systematic reviews, and publications investigating individually designed zirconia implants or involving patients with a significant health problem (ASA Physical Status 3 and above).

2.6. Selection of Studies

Duplicate articles were excluded, and the remaining articles were screened by title and abstracts for eligibility. Further examination regarding inclusion and exclusion was subsequently made by full-text analysis. The full text of any title or abstract that did not provide enough information regarding the inclusion criteria was also obtained. Any disagreement between the reviewers was discussed with a third author (T.B.). Cohen's kappa test was adopted to evaluate reviewers' agreement on the title and abstract selection.

2.7. Quality Assessment

The quality assessment of the included investigations was performed independently by two reviewers (M.R. and G.F.), based on the ARRIVE (Animals in Research: Reporting *In Vivo* Experiments)[(32)], considering the following items (Annex 2): Title; Abstract: summary; Introduction: background, primary and secondary objectives; Method: ethical statement, study design, experimental procedure, experiment animals, housing and animal care, sample size, allocation of animals to experimental groups, experiment outcomes, statistical analysis; Results: baseline data, numbers analyzed, outcomes and estimation, adverse events; Discussion: interpretation and scientific implications, generalizability and translation, funding. The maximum possible score by category was 36, graduated as follow: 0-12 (low-quality); 13-24 (moderate); 25-36 (high quality of assessment).

2.8. Data Extraction and Synthesis Methods

The reviewers extracted the data independently from the selected articles for further analysis using data extraction tables, which included the following parameters:

- Author(s), year of publication, and study design.
- Histomorphometry timing (months).
- Animal model and quantity used.
- Number of implants and location of implantation.
- Details of the implant, implant design (1-piece/2-piece), implant system, and implant surface morphology and/or treatment.
- Level of osseointegration (BIC %).

The meta-analysis involved the comparison of the data obtained from osseointegration. All analysis were performed using Excel (Microsoft, Redmond, U.S.A.), with a fixed or random effect model at a 5% significance level. Heterogeneity across the studies was quantified using the I^2 inconsistency test. Values above 75% were considered an indication of substantial heterogeneity. For those studies that confidential interval (CI) was not provided, a standard deviation (SD) value was used to calculate a CI.

3. RESULTS

3.Results

3.1. Study Selection

Through the initial search, with the terms and equations mentioned in the search strategy, 300 studies were identified from the electronic database search: 259 from PubMed/Medline®, 24 from PubMed Central® (PMC), and 17 from Embase®. Of the 300 articles initially found, 29 duplicates were removed, and the remaining 271 were reviewed by title, resulting in 60 articles included. Then, the abstract screening resulted in 30 articles to be evaluated by full-text assessment for further evaluation on the inclusion and exclusion criteria.

Finally, a total of 17 studies met the inclusion criteria and were included in the current review, and 13 articles were excluded based on exclusion criteria. (Figure 1; Table 3). All information collected from eligible articles is present in table 3 to table 9.

Regarding inter-examiner agreement between reviewers, the kappa values were 0.92 for the title screening, 0.95 for the abstract screening, and 1.0 for the full-text screening.

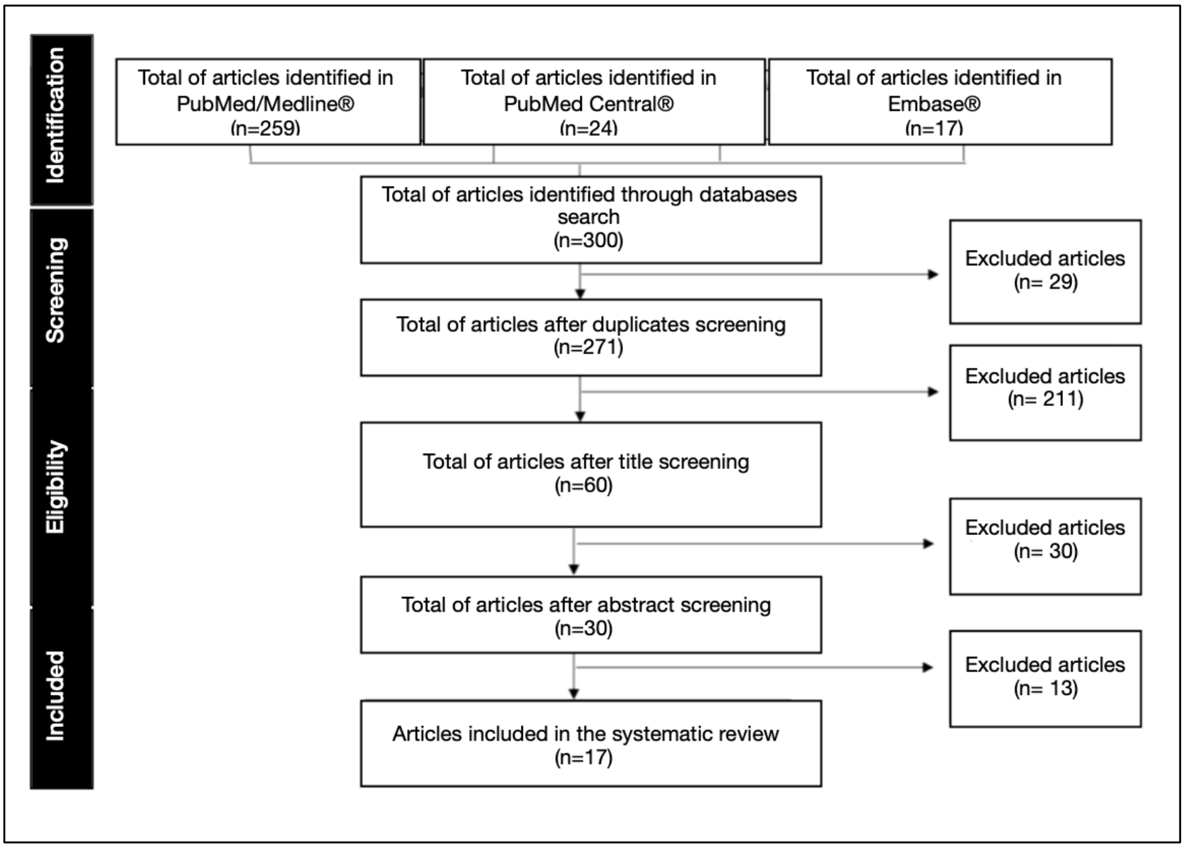

Figure 1- Flow diagram for the selection process for the included articles

Table 3- Reasons for exclusion of studies in the full-text screening	
Author/Year	**Reason for exclusion**
Kim et al, 2021	Insufficient data about study, implants and more
Chacun et al, 2021	Insufficient data about study and implants
Gahlert et al, 2012	Insufficient data about study and implants
Hoffmann et al, 2012	Insufficient data about study and implants
Martins et al, 2018	Insufficient data about study and implants
Ding et al, 2020	Insufficient data about implants
Kohal et al, 2016	Insufficient data about implants
Lee et al, 2013	Insufficient data about study and implants
Kubasiewicz-Ross et al, 2018	Insufficient data about study and implants
Möller et al, 2012	Insufficient data about study, implants and more
Gredes et al, 2014	Insufficient data about study, implants and more
Aboushelib et al, 2013	Insufficient data about study, implants and more
Igarashi et al, 2018	Insufficient data about study, implants and more

Table 4- Information about included articles after full-text screening		
First Author	**Year**	**Title**
Thomé G.[33]	2021	Osseointegration of a novel injection molded 2-piece ceramic dental implant: a study in minipigs.
Benic GI.[34]	2017	Guided bone regeneration at zirconia and titanium dental implants: a pilot histological investigation.
Janner SFM.[35]	2018	Bone response to functionally loaded, two-piece zirconia implants: A preclinical histometric study.

Table 4- Information about included articles after full-text screening (continued)		
First Author		**Title**
Thoma DS.[36]	2015	Histological analysis of loaded zirconia and titanium dental implants: An experimental study in the dog mandible.
Thoma DS.[37]	2019	Tissue integration of zirconia and titanium implants with and without buccal dehiscence defects—A histologic and radiographic preclinical study.
Salem NA.[38]	2013	Biomechanical and histomorphometric evaluation of osseointegration of fusion-sputtered zirconia implants.
Delgado-Ruiz RA.[39]	2014	Histologic and histomorphometric behavior of microgrooved zirconia dental implants with immediate loading.
Kohal RJ.[40]	2013	Osteoblast and bone tissue response to surface modified zirconia and titanium implant materials.
Liñares A.[41]	2016	Histological assessment of hard and soft tissues surrounding a novel ceramic implant: a pilot study in the minipig.
Mihatovic I.[42]	2017	Bone tissue response to experimental zirconia implants.
El Awadly TA.[43]	2020	A histomorphometric study on treated and untreated ceramic filled PEEK implants versus titanium implants: Preclinical in vivo study.
AlFarraj AA.[44]	2018	A comparative study of the bone contact to zirconium and titanium implants after 8 weeks of implantation in rabbit femoral condyles.
Chappuis V.[45]	2016	Osseointegration of Zirconia in the Presence of Multinucleated Giant Cells.
Calvo-Guirado JL.[46]	2015	Zirconia with laser-modified microgrooved surface vs. titanium implants covered with melatonin stimulates bone formation. Experimental study in tibia rabbits.
Park Y-S.[47]	2013	Peri-implant bone formation and surface characteristics of rough surface zirconia implants manufactured by powder injection molding technique in rabbit tibiae.
Mueller CK.[48]	2013	Analysis of the influence of the macro- and microstructure of dental zirconium implants on osseointegration: a minipig study.
Calvo-Guirado JL.[49]	2015	Histological and Histomorphometric Evaluation of Zirconia Dental Implants Modified by Femtosecond Laser versus Titanium Implants: An Experimental Study in Fox Hound Dogs.

3.2. Study Characteristics

Detailed information from the included articles is described in tables 5-8. The 17 publications selected were all preclinical in vivo investigations comparing osseointegration of zirconia vs titanium implants, published from 2013 through 2021. Only preclinical studies were chosen since the histologic assessment of osseointegration can only be done in a deceased population.

Most studies included investigated implants that were of two-piece design (n=10). Whereas some studies analyze implants with one-piece design (n=5) and with both type of designs (n=2).

The population included in these studies were dogs (27.55%), minipigs (14.28%), rats (14.28%), and rabbits (43.89%). The number of animals utilized ranges from 5 to 56. The implantation place varied from mandibles (36.82%), maxilla (9.04%), tibias (17.64%), skull (10.70%), and femur (25.80%).

The histomorphometry execution, specifically the interval between implantation and histologic examinations, varied from 0.25 to 12 months, with a mean period of 2.35 months. This parameter is critical for assessing the progress of the implants' osseointegration. It is advantageous if the implants' osseointegration improves with time.

A total of 370 titanium implants (Ti) and 537 zirconia implants (Zr) were evaluated. The materials of the zirconia implants varied from Zr (Zirconium), TZP (Tetragonal Zirconia Polycrystal), ATZ (Alumina Toughened Zirconia), Y-TZP (Yttrium-stabilized tetragonal zirconia) and ZrO_2 (Zirconium dioxide). The materials of the titanium implants were Ti-Grade 4 (commercially pure titanium grade 4) and cpTi (commercially pure titanium).

Table 5- Detailed Data of Included Studies

Study			Population		Zi Implants			Ti Implant		
Study/year	Study Design	Histomorphometry Timing (months)	n	Animal Model	n	Location	Materials	n	Location	Materials
One-piece design										
Delgado-Ruiz et al, 2014	Preclinical study	3	6	Foxhound dogs	16	Mandible	Zr	16	Mandible	Ti (grade 4)
					16		Zr (microgrooved)			
Liñares et al, 2016	Preclinical study	2	6	Minipig	9	Mandible	ZrO2	9	Mandible	Ti
El Awadly et al, 2020	Preclinical study	3	9	Mongrel dogs	9	Mandible	Zr	9	Mandible	Ti
					9		Zr (SCFP)			
Calvo-Guirado et al, 2015 (Dec)	Preclinical study	0,25	20	New Zealand rabbits	20	Tibia	Zr	20	Tibia	Ti
		1			20		Zr (melatonin)	20		Ti (melatonin)
Calvo-Guirado et al, 2015(Jun)	Preclinical study	1	6	American Fox Hound dogs	24	Mandible	Zr	24	Mandible	Ti
		3								
Two-piece design										
Thomé et al, 2021	Preclinical study	2	5	Minipig	15	Mandible	Zr	18	Mandible	Ti
Janner et al, 2018	Preclinical study	1	5	Canines	30	Mandible	Zr	30	Mandible	Ti
		3,5								
Thoma et al, 2019	Preclinical study	8	6	Mongrel dogs	12	Mandible	Zr	12	Mandible	Ti
		0,5			12		Zr	12		
AlFarraj et al, 2018	Preclinical study	2	16	New Zealand White rabbits	8	Femoral Condyles	Zr	8	Femoral Condyles	cpTi
					8		Zr (HA)	8		cpTi (HA)
Chappuis et al , 2016	Preclinical study	1	7	Goettinger miniature pigs	7	Maxilla	TZP	7	Maxilla	cpTi (grade 4)
		2			7		ATZ			
Park et al, 2013	Preclinical study	1	20	New Zealand White rabbits	27	Tibia	Zr	26	Tibia	Ti
					27		Zr (rough)			
Salem et al, 2013	Preclinical study	1	30	New Zealand White rabbits	30	Femoral Condyles	Zr	30	Femoral Condyles	Ti
		2			30		FS-Zr			
		3								
Kohal et al, 2013	Preclinical study	0,5	56	Sprague-Dawley rats	20	Femur	TZP-proc	20	Femur	TiUnite
		1			21		TZP-A-m	18		Ti-m
Mihatovic et al, 2017	Preclinical study	0,033	9	Beagle Dogs	8	Mandible	Zr (Z1)	18	Mandible	Ti
		0,5			8		Zr (Z2)			
		2,5			8		Zr (Z3)			
Mueller et al, 2013	Preclinical study	2	10	Miniature pigs	80	Frontal Sku	Y-TZP	17	Frontal Skull	cpTi
		4								
One- and Two-piece design										
Thoma et al, 2015	Preclinical study	12	6	Beagle dog	4	Mandible	Zr (VC; One-piece)	6	Mandible	Ti (grade 4; Two-piece)
					1		Zr (ZD; One-piece)			
					5		Zr (BPI; Two-piece)			
Benic et al, 2017	Preclinical study	3	7	Beagle dogs	7	Maxila	ZrO2 + DBBM (One-piece)	7	Maxila	Ti + DBBM granules (Two-piece)
					5		ZrO2 + DBBM-collagen (One-piece)			
					6		ZrO2 + DBBM block (One-piece)			

Table 6- Description of Zr Implants Investigated in Included Studies			
Study/year	Implant System/ Company	Material	Surface Morphology/ Treatment
One-piece design			
Delgado-Ruiz et al, 2014	White SKY, Bredent Medical GMBH & Co.	Zr	Sandblasted with alumina oxide particles
	White SKY, Bredent Medical GMBH & Co.	Zr (microgrooved)	Sandblasted with alumina oxide particles, treated with femtosecond laser pulses
Liñares et al, 2016	Institut Straumann AG, Basel	ZrO2	ZLA surface
El Awadly et al, 2020	BIO-HPP PEEK (Bio High Performance Polymer)	Zr	------
	BIO-HPP PEEK (Bio High Performance Polymer)	Zr (SCFP)	Sanblasted
Calvo-Guirado et al, 2015 (Dec)	WhiteSky"; Bredent Medical GmbH & Co. KG	Zr	Sandblasted
	WhiteSky"; Bredent Medical GmbH & Co. KG	Zr (melatonin)	Sandblasted,microgrooved by femtosecond laser and supplemented with MLT 5% in solution
Calvo-Guirado et al, 2015(Jun)	WhiteSky® //Bredent Medical® GmbH & Co. KG	Zr	Modified by femtosecond laser
Two-piece design			
Thomé et al, 2021	Neodent	Zr	Macro- rough
Janner et al, 2018	Institut Straumann AG,	Zr	Micro-rough // Sandblasted and acid-etched (hydrofluoric acid) (ZLA)
Thoma et al, 2019	AXIS HEXALOBE™ w/ modified surface; AXIS Biodental	Zr	Hydroxyapatite (HA) coating
	AXIS HEXALOBE™; AXIS Biodental	Zr	Moderately rough
AlFarraj et al, 2018	Medical grade Zr// Machinefabriek Jansen BV	Zr	------
	Medical grade Zr// Machinefabriek Jansen BV	Zr (HA)	Hydroxyapatite (HA) coating
Chappuis et al , 2016	Yttria-stabilizedzirconiawith 5% yttria // Zerafil-TZP, Dentalpoint AG	TZP	Fine granular surface
	Alumina-toughened zirconia with 4% yttria and 20% alumina // Zerafil-ATZ, Dentalpoint AG	ATZ	Fine granular surface
Park et al, 2013	Zirconia implant created using the PIM technique with an untreated mold, manufactured according to a proprietary process of Cetatech	Zr	-----
	Zirconia implant created using the PIM technique with a specially roughened mold, manufactured according to a proprietary process of Cetatech	Zr (rough)	-----
Salem et al, 2013	E grade 3 mol Y-TZP, Toso Inc, Tokyo, Japan	Zr	-----
	E grade 3 mol Y-TZP, Toso Inc, Tokyo, Japan	FS-Zr	Fusion- sputtering surface treatment
Kohal et al, 2013	VITA Zahnfabrik	TZP-proc	Sandblasted with Al2 O3 and acid-etched with hydrofluoric acid, nitric acid, and sulfuric acid
	VITA Zahnfabrik	TZP-A-m	Turned by machining
Mihatovic et al, 2017	Lava, 3M ESPE	Zr (Z1)	Sandblasted with grit sizes of 0.05 µm
	Lava, 3M ESPE	Zr (Z2)	Sandblasted with grit sizes of 0.11 µm
	Lava, 3M ESPE	Zr (Z3)	Sandblasted with grit sizes of 0.25 µm
Mueller et al, 2013	Institute for Bioprocessing and Analytical Measurement Techniques, Heilbad Heiligenstadt	Y-TZP	Sandblasted
One- and Two-piece design			
Thoma et al, 2015	Vitaclinical ceramic.implant// VITA Zahnfabrik H. Rauter GmbH & Co.	Zr (VC; One-piece)	-------
	Ziraldent// Metoxit AG, Thayngen	Zr (ZD; One-piece)	Microporous
	Bpisys.ceramic// BPI Biologisch Physikalische Implan- tate GmbH & Co.	Zr (BPI; Two-piece)	Nanostructured/ Hydrophilic surface
Benic et al, 2017	Vitaclinical// VITA Zahnfabrik	ZrO2 (One-piece) + DBBM	Sandblasted, acid etched, with hydrofluoric acid and annealin
		ZrO2 (One-piece) + DBBM-collagen	
		ZrO2 (One-piece) + DBBM block	

Table 7- Description of Ti Implants Investigated in Included Studies			
Study/year	**Implant System/ Company**	**Material**	**Surface Morphology/ Treatment**
One-piece design			
Delgado-Ruiz et al, 2014	Blue-sky®, Bredent Medical GMBH & Co	Ti (grade 4)	Sandblasted with alumina oxide and acid etched
Liñares et al, 2016	Institut Straumann AG, Basel	Ti	SLActive
El Awadly et al, 2020	I-FIX // Dentis company	Ti	Moderately rough
Calvo-Guirado et al, 2015 (Dec)	Blue SKY"; Bre- dent Medical GmbH & Co. KG	Ti	Sandblasted and acid-etched
	Blue SKY"; Bre- dent Medical GmbH & Co. KG	Ti (melatonin)	Sandblasted, acid-etched and supplemented with MLT 5% in solution
Calvo-Guirado et al, 2015(Jun)	Blue SKY®//Bredent Medical® GmbH & Co. KG	Ti	Sandblasted and acid-etched
Two-piece design			
Thomé et al, 2021	Neodent Alvim	Ti	Micro-roughness /Neoporous
Janner et al, 2018	Standard Plus Regular Neck; Institut Straumann AG	Ti (grade 4)	Sandblasted, acid- etched (SLA)
Thoma et al, 2019	CAMLOG® SCREW-LINE promote® plus, Camlog Biotechnologies	Ti	-------
AlFarraj et al, 2018	cpTi//Machinefabriek Jansen BV	cpTi	-----
	cpTi//Machinefabriek Jansen BV	cpTi (HA)	HA coating
Chappuis et al , 2016	cpTi grade 4, TST//Thommen Medical AG,	cpTi (grade 4)	Micro-roughness
Park et al, 2013	Machined surface titanium implant manufactured by Chaorum	Ti	--------
Salem et al, 2013	SLA, Tapered SP MTX, Zimmer Dental	Ti	Sandblasted and acid-etched
Kohal et al, 2013	TiUnite®, Nobel Biocare	TiUnite	Roughened by electrochemical anodization
	TiUnite®, Nobel Biocare	Ti-m	Turned by machining
Mihatovic et al, 2017	Tissue Level, Standard, Institute Straumann AG	Ti	Sandblasted with grits of 0.25–0.5 mm
Mueller et al, 2013	Institute for Bioprocessing and Analytical Measurement Techniques, Heilbad Heiligenstadt	cpTi	Sandblasted and acid etched
One- and Two-piece design			
Thoma et al, 2015	Straumann Standard Tissue Level implant/Institut Straumann AG	Ti (Grade 4; Two-piece)	Sandblasted, acid- etched (SLA)
Benic et al, 2017	OsseoSpeed™ S, ASTRA TECH Implant System, DENTSPLY Implants	Ti (Grade 4; Two-piece)	-------------------

Table 8- Detailed Data on Outcomes of Included Studies

Study/year	Histomorphometry Timing (months)	Zr Surface Morphology/Treatment	Ti Surface Morphology/Treatment	Zr Mean BIC (%)	Ti Mean BIC (%)
One-piece design					
Delgado-Ruiz et al, 2014	3	Sandblasted with alumina oxide particles	Sandblasted with alumina oxide and acid etched	48 ± 3%	57 ± 6%
		Sandblasted with alumina oxide particles, treated with femtosecond laser pulses		78 ± 5%	
Liñares et al, 2016	2	ZLA surface	SLActive	86.24 ± 9.71%	83.99 ± 3.61%
El Awadly et al, 2020	3	------	Moderately rough	30.9 ± 12.7%	54.0 ± 5.4%
		Sanblasted		51.1 ± 7.3%	
Calvo-Guirado et al, 2015 (Dec)	0,25	Sandblasted	Sandblasted and acid-etched	22.8 ± 1.5% (0,25m) // 37.5 ± 2.1% (1m)	25.4 ± 1.2% (0,25m) // 38.4 ± 1.8% (1m)
	1	Sandblasted,microgrooved by femtosecond laser and supplemented with MLT 5% in solution	Sandblasted, acid-etched and supplemented with MLT 5% in solution	28.9 ± 1.3% (0,25m) // 47.5 ± 2.2 (1m)	29.7 ± 2.4% (0,25m) // 39.2 ± 2.5% (1m)
Calvo-Guirado et al, 2015(Jun)	1	Modified by femtosecond laser	Sandblasted and acid-etched	44.68 ± 17.66% (1m) // 47.94 ± 16.15% (3m)	51.36 ± 12.03% (1m) // 61.73 ± 16.27% (3m)
	3				
Two-piece design					
Thomé et al, 2021	2	Macro-roughness	Micro-roughness/ Neoporous	77.8 ± 6.9%	80.7 ± 6.9%
Janner et al, 2018	1	Microrough / sandblasted and acid-etched (hydrofluoric acid) (ZLA)	Sandblasted, acid- etched (SLA)	75.58 ± 6.26	76.88 ± 2.84
	3,5			71.15 ± 7.03	69.76 ± 8.07
Thoma et al, 2019	0,5	Hydroxyapatite (HA) coating	------	46.9±12.14% (0,5m) // 81.48±14.26% (8m)	46.05±11.78% (0,5m) // 74.65±10.76% (8m)
	8	Moderately rough		35.77±8.14% (0,5m) // 75.34±17.95% (8m)	
AlFarraj et al, 2018	2	-----	-----	45.1 ± 14.8 %	45.5 ± 13.1%
		HA coating	HA coating	60.3 ± 17.1 %	59.8 ± 16.4 %
Chappuis et al , 2016	1	Fine granular surface	Micro-roughness	64.37% (1m) // 60.88% (2m)	82.30% (1m) // 79.86 % (2m)
	2			70.00 % (1m) // 57.04 % (2m)	
Park et al, 2013	1	-----	------	61.63 ± 12.39 %	42.54 ± 10.26 %
				64.42 ± 11.45%	
Salem et al, 2013	1	------	Sandblasted and acid-etched	56.94 ± 2.91% (1m) // 70.36 ± 2.88 % (2m) // 74.76 ± 3.85% (3m)	62.83 ± 1.97 % (1m) // 82.94 ± 2.79% (2m) // 86.77 ± 3.09% (3m)
	2	Fusion- sputtering surface treatment		69.66 ± 3.46% (1m) // 88.03 ± 2.94% (2m) // 89.09 ± 2.81% (3m)	
	3				
Kohal et al, 2013	0,5	Sandblasted with Al_2O_3 and acid-etched with hydrofluoric acid, nitric acid, and sulfuric acid	Roughened by electrochemical anodization	17.6 ±1.4% (0,5m) // 33.5 ± 4.1% (1m)	36.2 ±12.9% (0,5m) // 56.1 ± 15.8% (1m)
	1	Turned by machining	Turned by machining	30.9 ±10.1% (0,5m) // 46.6 ± 13.89% (1m)	23.2 ±6.3% (0,5m) // 39.4 ± 3.9% (1m)
Mihatovic et al, 2017	0,033	Sandblasted with grit sizes of 0.05 μm	Sandblasted with grits of 0.25–0.5 mm	25.06 ± 13.65% (0,033m) // 42.39 ± 23.44% (0,5m) // 49.71 ± 33.65% (2,5m)	42.26 ± 10.5% (0,033m) //62.19 ± 10.71% (0,5m) // 58.59 ± 17.24% (2,5m)
	0,5	Sandblasted with grit sizes of 0.11 μm		30.03 ± 9.97% (0,033m) // 44.46 ± 22.95% (0,5m) // 39.01 ± 0.0% (2,5m)	
	2,5	Sandblasted with grit sizes of 0.25 μm		28.97 ± 9.52% (0,033m) // 61.25 ± 17.71% (0,5m) // 69.57 ± 16.27% (2,5m)	
Mueller et al, 2013	2	Sandblasted	Sandblasted and acid etched	73.9 ±19.0% (2m) // 72.1 ± 20.0% (4m)	57.4 ±19.0% (2m) // 70.9% ± 19.0% (4m)
	4				
One- and Two-piece design					
Thoma et al, 2015	12	-------	Sandblasted, acid- etched (SLA)	87.71 ± 25.07 %	87.85 ± 13.59 %
		Microporous		78.58 ± 17.26 %	
		Nanostructured/ Hydrophilic surface		84.17± 25.07 %	
Benic et al, 2017	3	Sandblasted, acid etched, with hydrofluoric acid and annealin	--------	70 ± 19%	66 ± 27%
				69 ± 22%	
				77 ± 30%	

3.3 Quality assessment

The quality assessment of the included studies is presented in Table 9, and the categories and grading used to assess the quality of the experimental animal studies are described in Annex 2.

Amongst the 17 studies evaluated, all of them had accurate and concise titles. Only 3 studies had clearly accurate abstracts that included a summary of the background (score 2), and the rest of the 14 articles only lacked that topic (score 1).

Only 3 articles received a score of 1 after a full text read for the background developed in the introduction, due to the absence of information. All the other articles had clearly accurate introductions (score 2). Regarding the reference to the objectives in the introduction, all the studies had clear objectives (score 0).

Relating the methods of the studies, 7 articles (41.17%) had an incomplete concern with the ethical statement (score 1, possibly accurate) and the rest described an adequate ethical statement data (score 2). The study design was clearly well-established for 14 studies (82.35%) and the rest of the studies had a score of 1 (possibly accurate).

With regards to the experimental procedure, 3 studies (17.64%) lacked all the precise details of the procedure (score 1), but the others had a detailed experience procedure (score 2).

Five articles (29.41%) provided adequate information regarding the experimental animals, while 11 studies (64.71%) reported possible accurate information, and only 1 study[(40)] (5.88%) included insufficient data. With concern to housing and husbandry of the animals, only 3 studies (17.64%) provided adequate information, 10 articles (58.82%) partially provided enough data, and 4 studies (23.52%) had clearly insufficient information (score 0).

Nine articles (52.94%) provided clearly sufficient information about the sample size, while the other 8 (47.06%) provided incomplete data (score 1).

Regarding allocation of animals to experimental groups, only 2 studies (11.76%) didn't make an allocation. Experimental outcomes were well defined in 5 articles (29.41%), whereas the others were unclear or incomplete (score 1). All 17 included studies provided clear statistical methods.

Regarding the results, 12 articles (70.59%) provided baseline data characteristics and health status of animals, whereas the rest didn't provide sufficient information, especially regarding the health of the animals. Six studies (35.29%) had the number analyzed, whereas the rest didn’t.

The outcomes were clearly described in all 17 studies. Adverse events were properly reported in 10 studies (58.82%) and possibly accurately reposted in the rest of the studies, where the presence or absence of adverse events wasn’t reported.

Regarding the discussion of the studies, interpretation/scientific implications were well detailed in 7 studies (41.18%), while the rest had incomplete information. The relevance to human biology was well explicit in 13 studies (76.47%), whereas others had possibly accurate explicit relevance.

Finally, funding sources were clearly explicit in 7 articles (41.18%), possibly explicit in 3 articles (17.65%), and inaccurately reported in 7 articles (41.18%).

Only two articles had a score of moderate quality, with scores of 22 and 23. All other 15 articles were graduated as high quality of assessment, with scores from 25 to 31.

Table 9- Quality Assessment of Included Studies

Study/year	Categories of Quality Assessment*																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total Score
Delgado-Ruiz et al, 2014	1	2	2	0	2	1	2	1	0	2	1	1	2	0	1	2	2	2	2	0	26
Liñares et al, 2016	1	1	2	0	2	2	2	2	1	2	1	2	2	0	1	2	1	1	2	1	28
El Awadly et al, 2020	1	1	2	0	1	2	2	1	1	2	1	1	2	1	1	2	1	2	2	0	26
Calvo-Guirado et al, 2015 (Dec)	1	1	2	0	1	2	2	2	0	1	1	2	2	0	1	2	1	1	1	0	23
Calvo-Guirado et al, 2015(Jun)	1	1	2	0	2	2	2	1	1	2	1	1	2	0	1	2	2	1	2	0	26
Thomé et al, 2021	1	1	2	0	2	2	2	2	1	2	0	2	2	1	2	2	2	1	2	2	31
Janner et al, 2018	1	1	2	0	2	2	2	1	1	1	1	1	2	1	2	2	2	2	2	2	30
Thoma et al, 2019	1	1	2	0	2	2	2	1	1	2	1	2	2	1	1	2	2	2	2	2	31
AlFarraj et al, 2018	1	2	2	0	1	2	1	1	1	2	1	1	2	1	1	2	2	2	2	0	27
Chappuis et al , 2016	1	2	2	0	2	2	2	1	0	1	1	1	2	1	1	2	1	1	2	2	27
Park et al, 2013	1	1	2	0	1	2	2	1	2	2	0	1	2	1	1	2	1	1	2	1	26
Salem et al, 2013	1	1	2	0	1	1	1	1	2	1	1	1	2	1	1	2	2	2	2	0	25
Kohal et al, 2013	1	1	2	0	2	1	2	0	0	1	1	1	2	1	2	2	2	2	2	1	26
Mihatovic et al, 2017	1	1	1	0	1	2	2	1	1	2	1	1	2	1	2	2	2	1	1	2	27
Mueller et al, 2013	1	1	1	0	2	2	1	2	1	1	1	1	2	0	1	2	1	1	1	0	22
Thoma et al, 2015	1	1	1	0	2	2	2	1	1	1	1	1	2	1	2	2	2	1	2	2	28
Benic et al, 2017	1	1	2	0	1	2	2	2	2	1	1	2	2	1	2	2	1	1	1	2	29

* Categories of Quality Assessment: Title (1); Abstract: summary (2); Introduction: background (3), primary and secondary objectives (4); Method: ethical statement (5), study design (6), experimental procedure (7), experiment animals (8), housing and animal care (9), sample size (10), allocation of animals to experimental groups (11), experiment outcomes (12), statistical analysis (13); Results: baseline data (14), numbers analyzed (15), outcomes and estimation (16), adverse events (17); Discussion: interpretation and scientific implications (18), generalizability and translation(19), funding (20). Score Graduation: 0-12 (low-quality); 13-24 (moderate); 25- 36 (high quality of assessment).

3.4. Osseointegration Rates

The osseointegration rates of zirconia and titanium implants were compared in all the investigations using the bone-to-implant percentage (BIC %). The rates of osseointegration of zirconia and titanium implants were similar. The percentual average of osseointegration for Zr was 55.51% (min. 17,6% and max. 89.09%), whereas Ti was 58.50% (min. 23,2% and max. 87.85%).

One- and two-piece Zr had a similar osseointegration rate to one- and two-piece Ti. In all the studies, except in Janner et al.(35), the osseointegration rate of both types of implants increased with time and reached similar values.

High heterogeneity was found between studies at 1 and 3 months. Additionally, few comparative studies were found after 3 months of analysis, which made any kind of statistical analysis unfeasible. There was no statistical difference between studies at 2 months ($p = 0.672$). While for the studies analyzed at 1 month and 3 months, statistically significant data of $p < 0.001$ were found for both. (Figure 2)

3.4.1. Dogs

In 8 studies, dogs were used as animal models to investigate osseointegration rates.(34–37,39,42,43,49) Seven studies used the mandible as the location of implantation, except Benic et al.(34), that implanted in the maxilla.

Thoma et al.(36), has reported the greatest osseointegration rate of titanium implants (87.85 ± 13.59 %) and highest of zirconia implants (87.71 ± 25.07 %), among these investigations.

3.4.2. Minipigs

Percentual of BIC was investigated in 4 studies that used minipigs as animal models.(33,41,45,48) The implantation location varied from mandible, maxilla, and skull.

The investigation of Liñares et al.(41) reported the highest osseointegration of zirconia implants (86.24 ± 9.71%) and titanium implants (83.99 ± 3.61%), among these studies.

3.4.3. Rats

Kohal et al.[40] was the only investigation included that used rats as animal models. In this study, the implantation location was the femur and the histomorphometry timing was 0,5 and 1 month. The highest BIC % of the zirconia implants investigated was 46.6 ± 13.89% (1 month), for a zirconia implant (VITA Zahnfabrik) turned by machining. The greatest osseointegration rate of the titanium implants was 56.1 ± 15.8% (1 month), for a roughened by electrochemical anodization implant (TiUnite®).

3.4.4. Rabbits

There were 4 studies that utilized rabbits as animal models. [38,44,46,47] From these studies, the tibia and the femur were the implantation location selected. Based on these studies, Salem et al.[38] reported the highest osseointegration rate for zirconia and titanium implants, 89.09 ± 2.81% and 86.77 ± 3.09%, respectively.

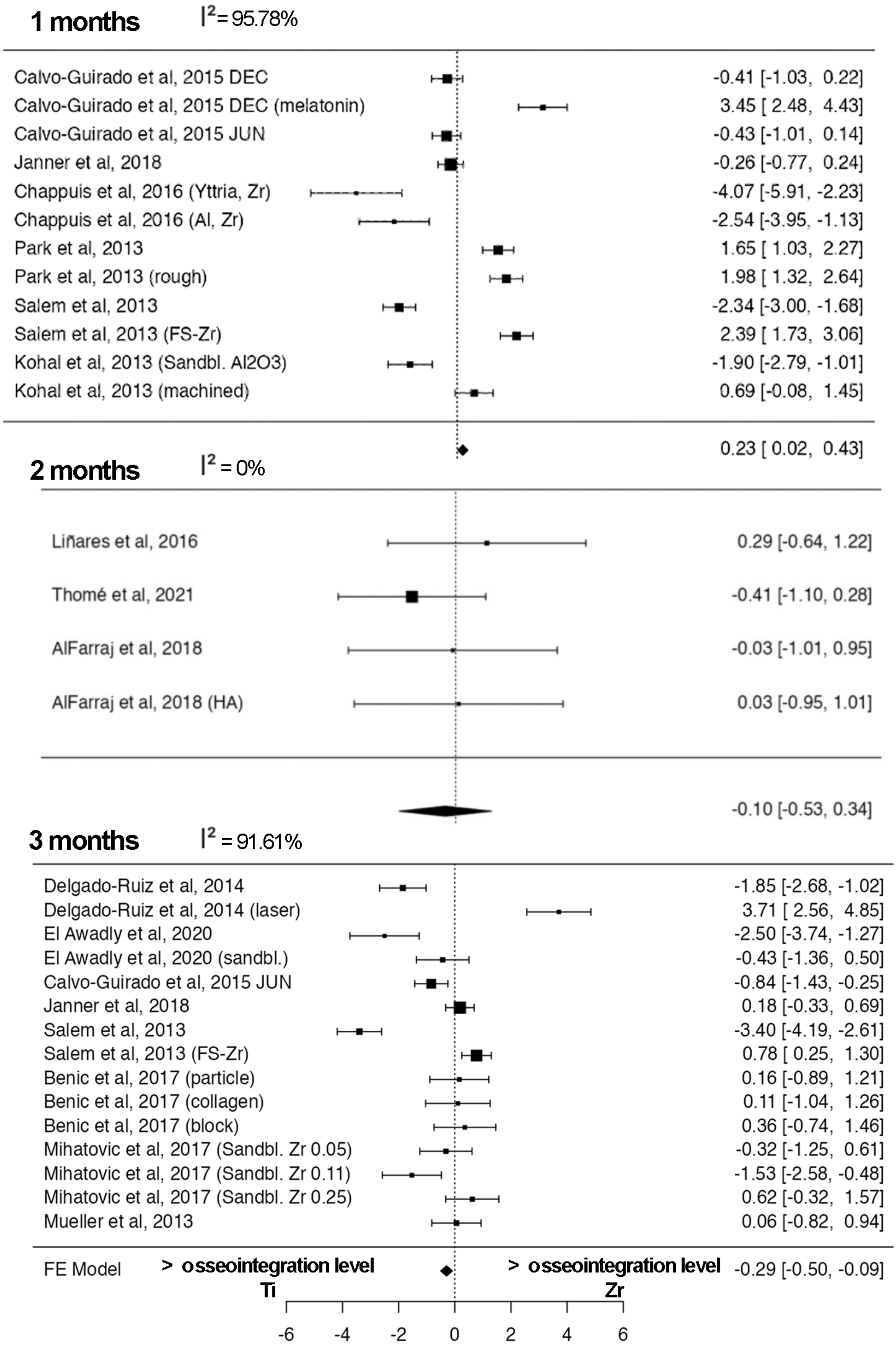

Figure 2- Forest plot for osseointegration at 1, 2, and 3 months of histomorphometry (RE Model: Random Effect Model).

4. DISCUSSION

4. Discussion

Titanium implants, the gold standard, offer a good survival rate, excellent strength, biocompatibility, and osseointegration. However, they can produce unsatisfactory results in aesthetic rehabilitation. As a result, there has been a rise in research into zirconia implants due to their characteristics such as ivory color, low elasticity modulus, high flexural strength, toughness, radiopacity, biocompatibility, low plaque affinity, good osseointegration, and a satisfactory survival rate.(18)

One of the most important factors determining the lifespan of a dental implant is osseointegration. As a result, this systematic review was carried out to examine the possible recommendation for the usage of zirconia implants in all clinical scenarios, beyond the esthetic-driven scenarios. The objective of this systematic review is to evaluate and compare the osseointegration rates of zirconia versus titanium implants, through histologic analysis.

4.1. Osseointegration Rates

Research has demonstrated that dental implant materials (Zr and Ti) do not significantly influence the osseointegration rates of implants.(50–52) Indeed, a recent systematic review of animal studies by Roehling et al.(53) reported similar results for mean BIC % in comparison to the present study, specifically, 59.1% for titanium implants and 55.9% for zirconia implants. In addition, Pieralli et al.(50) reported a mean BIC % of 60.70% for titanium implants and zirconia implants showed a reduced BIC % of -3.47%, in other words, 57.23%.

Other research, however, has shown that titanium has better osseointegration than zirconia when only comparing the material of the implant. On the other hand, after surface treatment, zirconia displays about the same rate of osseointegration as titanium. As a result, we may deduce that surface roughness is the most important determinant of osseointegration.(21)

Moreover, when analyzing the implant's primary body material (Zr and Ti), the surface treatments should be comparable, because the variation in surface roughness has a bigger influence on osseointegration rates than the material itself.(54) Most included studies in the present systematic review investigated different types of implant surfaces to research their influence on osseointegration.

However, when comparing Zr and Ti implants with similar surface treatment there is not a significant difference in BIC %. For instance, AlFarraj et al.(44) reported an osseointegration rate of 60.3 ± 17.1 % for zirconia implants and 59.8 ± 16.4 % for titanium implants, with the same surface treatment (HA coating) and histomorphometry timing (2 months).

Many surface features, such as topography, wettability, and coatings, can influence early osseointegration. According to research, isotropic (with irregularities without specific direction) and moderately rough surfaces (1-2 µm) on implants are ideal for having a higher BIC%. Manufacturing processes like machining, acid-etching, anodization, sandblasting, grit-blasting, and other coating methods can be used to generate this form of microtopography. Furthermore, microroughness is intended to give greater biomechanical interlocking. On the other hand, nanoroughness is believed to benefit the adhesion of the first proteins that contact the implant surface.(13,55–57)

Salem et al.(38), possessed the maximum mean BIC % result of zirconia implants of 89.09% at 3 months of histomorphometry. This Zr implant (E grade 3 mol Y-TZP, Toso Inc.) got fusion-sputtering surface treatment, resulting in a microrough surface that improved bone apposition at the bone to implant interface. Spraying a suspension of zirconia mixture made of 5 g ultrafine zirconia powder (1-5m) and 10 ml ethyl alcohol (70%) was used for this surface treatment. Scanning electron microscope (SEM) pictures indicated a rough microstructure (Ra=14±5), with a granular surface formed of spherical particles (height 14 to 18 µm) fused to the implants' outer surface. Although this surface treatment is new and requires additional research, particularly long-term findings on its performance, it has the potential to be an ideal surface treatment for implants.(38,58)

Thoma et al.(36), reported the maximum mean osseointegration rate of titanium implants of 87.85% at 12 months of histomorphometry. This Ti implant (Straumann Standard Tissue Level implant) had a sandblasted, acid-etched (SLA) surface treatment. The surface morphology of the implant is normally rough and irregular following sandblasting, but after acid etching, the surface becomes more uniform, and small micro pits emerge.(59) This surface roughening approach is typically applied in the implant fabrication industry since it has been shown to contribute to a higher BIC percent (50-60%) compared to titanium plasma spray treatment (30-40%), for example.[59,60]

Furthermore, the osseointegration rates of implants rise with time in most of the included studies. This is related to the bone remodulation process that occurs during the shift to secondary stability.[12] In the majority of included studies, titanium implants exhibited higher osseointegration rates throughout the early healing phase. However, in most cases, there was no significant difference in % BIC between titanium and zirconia implants throughout this period.

Another aspect to consider is the effect of implant loading. Most of the included studies didn't investigate osseointegration in loaded implants. Delgado-Ruiz et al.[39] investigated the behavior of zirconia implants with immediate loading. They concluded that BIC% was higher in immediately loaded implants of both zirconia and titanium groups.

Finally, although we are comparing the osseointegration of two materials, zirconia and titanium, we must not overlook additional elements that have a massive effect on osseointegration. Surface properties impact primary stability and, more particularly, the lifetime of dental implants. Additionally, the most important aspect influencing primary stability and the implant's capacity to tolerate loading following osseointegration is the implant's design.[61]

4.2. Animal Models

Preclinical *in vivo* research is critical in implantology research for determining biological relevance, biofunctionality, biocompatibility, and clinical effectiveness of a study implant.[52]

Because there are various discrepancies between the reactions of other animal species and humans to implant treatment, the most comparable model to the human organism must be used. Furthermore, the place of implantation, the age of the model, and the blood supply of the site, which differs by species, must all be evaluated.[52]

The most often used animal models in implantology are rats, rabbits, dogs, pigs, sheep, and goats.[52] No species meets all the criteria for an ideal model. Each model, however, can be recommended to use for investigation. The rabbit is one of the most used models, however, it has the fewest resemblance to human bone. The pig has a striking resemblance to the human bone; however, issues may arise because of its size and ease of handling. In this regard, the dog and sheep/goat appear to be more promising as animal models for investigating bone implant materials.(62) In fact, most included articles in the present systematic review used dogs as an animal model (n=8).

Finally, because of the variety of animal models that might be utilized in implant research, standardizing evaluation metrics is problematic. Indeed, there was some disparity in the current study's findings between investigations using different animal models. Therefore, to properly analyze and compare research outcomes, attempts to standardize preclinical animal experiments are necessary.(50)

Furthermore, even though there are just a few systematic reviews of pre-clinical animal studies, they may help to enhance the quality of future animal-based studies and offer an evidence-based transition between preclinical and clinical studies.(50)

4.3. Limitations of the study

A limitation of the present systematic review is that only preclinical studies were chosen because they are the most effective way to assess osseointegration of implants using histology. The studies included were the only ones that met the inclusion criteria, specifically comparing osseointegration rates of zirconia implants with titanium implants.

As a result of the preclinical nature of these findings, all data and results must be critically analyzed, and clinical trials assessing osseointegration of titanium and zirconia implants are required to scientifically support the recommendation of increased usage of zirconia implants.

Furthermore, another limitation of this study is the heterogeneity found between studies at 1 and 3 months.

Finally, another limitation of the current systematic review is that not all the included articles reported information about the surface treatment of the implant. This prevented appropriate comparison of osseointegration outcomes.

4.4. Clinical Significance

The current systematic review has offered additional scientific investigation on the osseointegration rates of zirconia vs titanium implants. More research, particularly clinical studies, is required to properly analyze the scientific data in order to expand the use of zirconia in implantology.

5. CONCLUSIONS

5. Conclusions

Within the limitation of this study, osseointegration results suggest that Zr implants are a viable option for oral rehabilitation. Zirconia implants have presented a similar level of osseointegration compared to the gold standard (Titanium implants). Nonetheless, as these results came from preclinical studies, all data must be carefully analyzed and clinical trials assessing osseointegration of Ti and Zr implants are necessary to further establish the effectiveness of zirconia implants.

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ANNEXES

ANNEXES

Annex 1: PROSPERO Registration

Registered	Title	Type	Review status
15/03/2021	Comparison between zirconia and titanium dental implants: a systematic review and meta-analysis [CRD42021236781]		Review Ongoing

Annex 2. Categories and grading used to assess the quality of the experimental animal studies.

ITEM	DESCRIPTION	GRADE
1	**Title**	0 = inaccurate/not concise 1 = accurate and concise
2	**Abstract** Summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
3	**Introduction** Background-objectives, experimental approach and rationale, relevance to human biology	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
4	**Introduction** Objectives-primary and secondary	0 = clear 1 = not clear
5	**Methods** Ethical statement-nature of the review permission, relevant licenses, national and institutional guidelines for the care and use of animals	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
6	**Methods** Study design-number of experimental and control groups, any steps taken to minimize bias (i.e., allocation concealment, randomization, blinding)	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
7	**Methods** Experimental procedure-precise details (i.e., how, when, where, why)	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
8	**Methods** Experimental animals-species, strain, sex, developmental stage, weight, source of animals	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
9	**Methods** Housing and husbandry-conditions and welfare-related assessment interventions (i.e., type of cage, bedding material, number of cage companions, light/dark cycle, temperature, access to food and water)	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
10	**Methods** Sample size-total number of animals used in each experimental group, details of calculation methods	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
11	**Methods** Allocation of animals to experimental groups-randomization or matching, order in which animals were treated or assessed	0 = no 1 = yes
12	**Methods** Experimental outcomes-definition of primary and secondary outcomes	0 = no 1 = unclear/not complete 2 = yes
13	**Methods** Statistical methods-details and unit of analysis	0 = no 1 = unclear/not complete 2 = yes
14	**Results** Baseline data characteristics and health status of animals	0 = no 1 = yes
15	**Results** Number analyzed-absolute numbers in each group included in each analysis, explanation for exclusion	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
16	**Results** Outcomes and estimation-results for each analysis with a measure of precision, as standard error or confidence interval?	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
17	**Results** Adverse events-details and notifications for reduction	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
18	**Discussion** Interpretation/scientific implications-study limitations including animal model, implications for the 3Rs	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
19	**Discussion** Generalizability/translation-relevance to human biology	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
20	**Discussion** Funding-sources, role of the funders	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate