Histologic Osseointegration Level Comparing Titanium and Zirconia Dental Implants: Meta-analysis of Preclinical Studies

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Purpose: To assess the literature comparing histologic levels of osseointegration for titanium vs zirconia dental implants. ***Materials and Methods:*** This systematic review was conducted following the PRISMA guidelines and was registered in PROSPERO (CRD42021236781). Electronic and manual searches were carried out through the PubMed/MEDLINE, PubMed Central, and Embase databases with a platform-specific search strategy combining controlled terms (MeSH and Emtree) and text words. The articles were selected by two independent investigators who evaluated the articles based on the criteria for eligibility. ***Results:*** A total of 17 articles were included. All were preclinical studies. The populations included dogs (27.55%), minipigs (14.28%), rats (14.28%), and rabbits (43.89%); and the implantation site varied among the mandible (36.82%), maxilla (9.04%), tibia (17.64%), skull (10.70%), and femur (25.80%). A total of 370 titanium (Ti) implants and 537 zirconia (Zr) implants were evaluated. The average osseointegration (% bone-to-implant contact) for Zr was 55.51% (17.6% to 89.09%), and for Ti was 58.50% (23.2% to 87.85%). There was no statistical difference between studies at the 2-month follow-up ($P = .672$), but this difference was significant at 1 and 3 months ($P < .001$). ***Conclusions:*** Within the limitations of this review, Zr implants had a similar level of osseointegration compared to Ti implants. Nonetheless, because these findings are based on preclinical research, all data must be carefully examined. *Int J Oral Maxillofac Implants 2023;38:667–680. doi: 10.11607/jomi.10142*

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Implant dentistry has progressed from an experimental procedure to a highly predictable treatment option for replacing lost teeth with implant-supported prostheses in fully and partially edentulous patients.[1] The fundamental goals of implant therapy are to obtain satisfactory results for function, esthetics, and phonetics with high predictability, long-term stability, and minimal risk of complications.[1]

To achieve this, direct contact must be established between remodeled bone and a dental implant without the interposition of fibrous tissues; ie, osseointegration must occur. In clinical terms, *osseointegration* refers to an implant's stability and functional ankylosis in bone,[2] permitting a sustained transfer and distribution of load from the implant to the bone tissue. Biologically, osseointegration has been proposed as an immune-driven process that results in new bone production. Research shows implants have a tolerogenic balance with peri-implant tissues resulting in a foreign body equilibrium response. As a result, the bone-to-implant contact (BIC) is thought to be regulated by the immune response using the same processes as in tissue healing and regeneration. To summarize, the immune system first recognizes the implant as a foreign body, then forms bone around it as a defensive reaction to shield the implant from the surrounding tissues.[3–5]

Furthermore, research has shown that the long-term maintenance of foreign body equilibrium is key to the longevity of implant osseointegration. In fact, a balance between antimicrobial and proinflammatory M1 macrophages and anti-inflammatory and proregenerative M2 macrophages has been correlated with wound healing, regeneration, and osseointegration.[3,6] Moreover, the dynamic process of osseointegration happens during the implant's transition from primary stability to secondary stability. Secondary stability is built up

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beginning with the first apposition of new bone onto the implant surface.[7]

Diverse implant materials, designs, and surface properties (topographic, chemical, mechanical, and physical) have different implications for osseointegration. Currently, the most often used dental implant materials are titanium (Ti) and zirconium dioxide (ie, zirconia [Zr]). Ti implants have a high survival rate (96.4% after a 10-year observation period),[8] but also a few drawbacks. First, Ti implants do not always produce good esthetic results due to discoloration of the peri-implant soft tissues, which results in a grayish shade and mucosal recession.[8,9] Second, tribocorrosion occurs when free metallic ions are released from the Ti implant surface. T-cells may mediate type IV hypersensitivity and inflammatory reactions due to this process, so Ti corrosion may affect implant osseointegration by directly activating osteoclasts and osteoblasts or stimulating inflammatory cytokine secretion. To summarize, Ti can cause proinflammatory and hypersensitivity/allergic effects, leading to contact dermatitis, pain, swelling, delayed healing, and, in the end, implant failure.[8,10–12]

As a result, Zr implants are a viable option for esthetic-driven rehabilitative procedures. Zr has a high osseointegration rate, and one-piece Zr implants have a high mean survival rate (> 98%), low marginal bone loss after a 5-year follow-up, and less plaque accumulation in addition to good light transmission properties. The ivory coloration of Zr allows for better esthetic results with the mucosa in anterior implants,[9,11,13–15] resulting in better soft tissue management and a more pleasing appearance.[16] Despite this, Zr implants have some disadvantages, such as low-temperature degradation, which reduces the implant's strength, toughness, and density.[11,13,17]

In addition, research has shown that Zr requires surface modification to achieve a similar osseointegration rate to titanium implants.[18] Thereby, microrough Zr implants have a similar osseointegration capacity compared to microrough Ti implants under unloaded and loaded settings. On the other hand, Ti exhibits a faster initial osseointegration process than Zr.[19,20] While Zr implants are a promising treatment option, more research on osseointegration is required.

Thus, this systematic review aimed to evaluate and compare the histologic levels of osseointegration between Ti and Zr dental implants.

MATERIALS AND METHODS

This systematic review was conducted following the PRISMA guidelines and was registered in PROSPERO (CRD42021236781). The focused question was determined using the population, intervention, comparison, and outcome (PICO) strategy[21–23] and was as follows: In dental implants placed in bone (P), do zirconia implants (I) vs titanium implants (C) exhibit different osseointegration outcomes at the histologic level (O)?

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 (Appendix Tables 1 and 2; all appendices can be seen in the online version of this article at www.quintpub.com/journals). An additional manual search was performed in the references of included articles to identify relevant publications.

Only articles published in the English language from February 2012 up to February 2022 were included. Two reviewers (M.J.S.R. and G.V.O.F.) independently performed the electronic and manual searches. The publications obtained from the search of all mentioned databases were imported into a reference management software (EndNote X9, Thomson Reuters) and subsequently screened.

Inclusion Criteria

This systematic review included clinical trials, prospective and retrospective clinical studies, case series, and preclinical studies reporting histologic analysis of the osseointegration of Ti and/or Zr implants. Articles published between February 2012 and February 2022 analyzing Ti and/or Zr dental implants and reporting detailed information on the implant(s) used and regarding osseointegration were included. In the case of multiple studies involving the same patient cohort, only the publication with the most extended follow-up was included.

Exclusion Criteria

Studies that did not meet all inclusion criteria were excluded. Reports based on questionnaires, interviews, case reports, and in vitro studies were rejected, as well as any type of review or publication investigating individually designed Zr implants or involving patients with a significant health problem (ASA Physical Status 3 and above).

Selection of Studies and Data Extraction

Duplicate articles were excluded, and the remaining articles were screened by title and abstract for eligibility. Further examination regarding inclusion and exclusion was undertaken by full-text analysis. The full text of any article that did not provide enough information regarding the inclusion criteria in the title and/or abstract was also obtained. Any disagreement between reviewers was discussed with a third author (T.B.). Cohen kappa

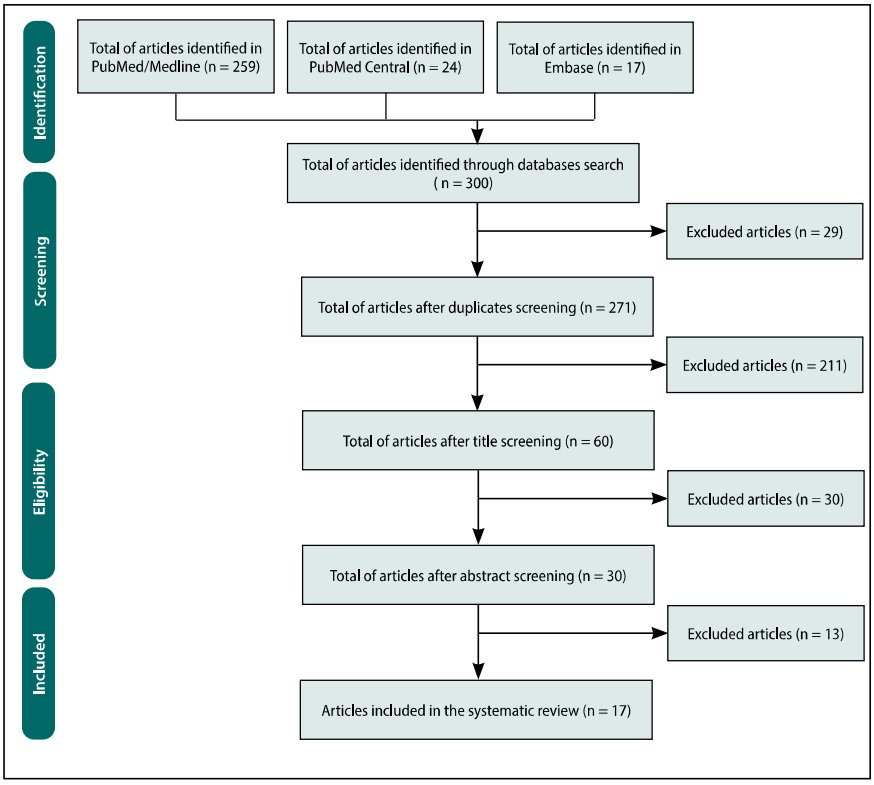

Fig 1 Flow diagram showing the selection process for the included articles.

test was adopted to evaluate the reviewers' agreement on the title and abstract selection.

The reviewers extracted the data independently from the selected articles for further analysis using data extraction tables that included the following parameters: author(s), year of publication, and study design; histology period (months); animal model and quantity used; number of implants and location of implantation; details of the implant, such as implant design (one-piece/two-piece), implant system, and implant surface morphology and/or treatment; and the percentage of osseointegration (%BIC).

Quality Assessment

The quality assessment of the included investigations was performed independently by two reviewers (M.J.S.R. and G.V.O.F.) based on the ARRIVE guidelines[24] considering the following items (Appendix Table 3):

- Title
- Abstract: summary
- Introduction: background, primary and secondary objectives
- Methods: 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 for each category was 36, and the rating scheme was as follows: 0–12 (low quality); 13–24 (moderate); 25–36 (high quality).

Statistical Analysis

The meta-analysis involved comparison of the data on osseointegration obtained from eligible studies. All analyses were performed using Microsoft Excel with a fixed- or random-effects model at a 5% significance level. Heterogeneity across studies was quantified using the I^2 inconsistency test. Values above 75% were considered to indicate substantial heterogeneity. For studies in which a CI was not provided, the SD value was used to calculate a CI.

RESULTS

Study Selection

A total of 300 studies were identified from the electronic databases in the initial search strategy: 259 from PubMed/MEDLINE, 24 from PMC, and 17 from Embase. Of the 300 articles, 29 duplicates were removed, and the remaining 271 were reviewed by title. The 60 articles remaining after title screening were screened by abstract, leaving 30 articles for full-text assessment. Finally,

Table 1 Detailed Data of Included Studies

Study			Population		Zi implants			Ti implants		
Study	Study design	Histomorphometric follow-up (mo)	No.	Animal model	No.	Location	Material(s)	No.	Location	Materials
One-piece design										
Delgado-Ruiz et al, 2014[29]	Preclinical study	3	6	Foxhound dogs	16 16	Mandible	Zr Zr (microgrooved)	16	Mandible	Ti (grade 4)
Liñares et al, 2016[34]	Preclinical study	2	6	Minipigs	9	Mandible	ZrO_2	9	Mandible	Ti
El Awadly et al, 2020[31]	Preclinical study	3	9	Mongrel dogs	9 9	Mandible	Zr Zr (SCFP)	9	Mandible	Ti
Calvo-Guirado et al, 2015 (Dec)[40]	Preclinical study	0.25 1	20	New Zealand rabbits	20 20	Tibia	Zr Zr (covered with melatonin)	20 20	Tibia	Ti Ti (covered with melatonin)
Calvo-Guirado et al, 2015 (Jun)[32]	Preclinical study	1 3	6	American Foxhound dogs	24	Mandible	Zr	24	Mandible	Ti
Two-piece design										
Thomé et al, 2021[33]	Preclinical study	2	5	Minipigs	15	Mandible	Zr	18	Mandible	Ti
Janner et al, 2018[25]	Preclinical study	1 3.5	5	Canines	30	Mandible	Zr	30	Mandible	Ti
Thoma et al, 2019[28]	Preclinical study	8 0.5	6	Mongrel dogs	12 12	Mandible	Zr Zr	12 12	Mandible	Ti
AlFarraj et al, 2018[39]	Preclinical study	2	16	New Zealand white rabbits	8 8	Femoral condyles	Zr Zr (hydroxyapatite)	8 8	Femoral Condyles	cpTi cpTi (hydroxyapatite)
Chappuis et al, 2016[35]	Preclinical study	1 2	7	Goettinger miniature pigs	7 7	Maxilla	TZP ATZ	7	Maxilla	cpTi (grade 4)

SCFP = sandblasted ceramic-filled PEEK; cpTi = commercially pure titanium.

13 articles were excluded after full-text reading, and 17 studies were included (Fig 1 and Appendix Table 4). Regarding interexaminer agreement between reviewers, the kappa values were 0.92 for title screening, 0.95 for abstract screening, and 1.0 for full-text screening.

Study Characteristics

Detailed information from the included articles is described in Tables 1 to 4. The 17 publications were preclinical in vivo investigations comparing osseointegration of Zr vs Ti implants. Only preclinical studies were found because histologic assessment of osseointegration can only be done in a deceased population. Most studies included implants that were of a two-piece design (n = 10), but some studies analyzed implants with a one-piece design (n = 5) and with both types of designs (n = 2).

The populations included in these studies were dogs (27.55%), minipigs (14.28%), rats (14.28%), and rabbits (43.89%). The number of animals utilized ranged from 5 to 56. The implantation locations were the mandible (36.82%), maxilla (9.04%), tibia (17.64%), skull (10.70%), and femur (25.80%). The histomorphometric analysis, specifically the interval between implantation and histologic examination, varied from 0.25 to 12 months, with a mean period of 2.35 months. This parameter is

Table 1 Detailed Data of Included Studies (cont)

Study			Population		Zi implants			Ti implants		
Study	Study design	Histomorphometric follow-up (mo)	No.	Animal model	No.	Location	Material(s)	No.	Location	Materials
Park et al, 2013[41]	Preclinical study	1	20	New Zealand white rabbits	27 27	Tibia	Zr Zr (rough)	26	Tibia	Ti
Salem et al, 2013[38]	Preclinical study	1 2 3	30	New Zealand white rabbits	30 30	Femoral condyles	Zr FS-Zr	30	Femoral Condyles	Ti
Kohal et al, 2013[37]	Preclinical study	0.5 1	56	Sprague-Dawley rats	20 21	Femur	TZP-proc TZP-A-m	20 18	Femur	TiUnite Ti-m
Mihatovic et al, 2017[30]	Preclinical study	0.033 0.5 2.5	9	Beagle dogs	8 8 8	Mandible	Zr (Z1) Zr (Z2) Zr (Z3)	18	Mandible	Ti
Mueller et al, 2013[36]	Preclinical study	2 4	10	Miniature pigs	80	Frontal skull	Y-TZP	17	Frontal Skull	cpTi
One- and two-piece designs										
Thoma et al, 2015[27]	Preclinical study	12	6	Beagle dog	4 1 5	Mandible	Zr (one-piece) Zr (one-piece) Zr (two-piece)	6	Mandible	Ti (grade 4, two-piece)
Benic et al, 2017[26]	Preclinical study	3	7	Beagle dogs	7 5 6	Maxila	ZrO_2 + DBBM (one-piece) ZrO_2 + DBBM collagen (one-piece) ZrO_2 + DBBM block (one-piece)	7	Maxila	Ti + DBBM granules (two-piece)

FS-Zr = fusion-sputtered zirconia implants; TZP-proc = sandblasted and acid-etched zirconia; TZP-A-m = machined zirconia; Z1, Z2, Z3 = three different surface roughnesses.

Table 2 Description of Zr Implants Investigated in the Included Studies

Study	Implant system/	Material	Surface morphology/treatment
One-piece design			
Delgado-Ruiz et al, 2014[29]	whiteSKY, Bredent	Zr	Sandblasted with alumina oxide particles
	whiteSKY, Bredent	Zr (microgrooved)	Sandblasted with alumina oxide particles, treated with femtosecond laser pulses
Liñares et al, 2016[34]	Institut Straumann	ZrO_2	ZLA surface
El Awadly et al, 2020[31]	BioHPP PEEK (Bio High Performance Polymer), Bredent	Zr	–
	BioHPP PEEK (Bio High Performance Polymer), Bredent	Zr (SCFP)	Sandblasted
Calvo-Guirado et al, 2015 (Dec)[40]	whiteSKY, Bredent	Zr	Sandblasted
	whiteSKY, Bredent	Zr (melatonin)	Sandblasted, microgrooved by femtosecond laser, and supplemented with MLT 5% in solution
Calvo-Guirado et al, 2015 (Jun)[32]	whiteSKY, Bredent	Zr	Modified by femtosecond laser

ZLA = zirconia sandblasted and acid-etched surface; MLT = melatonin.

Table 2 Description of Zr Implants Investigated in the Included Studies (cont)

Study	Implant system/	Material	Surface morphology/treatment
Two-piece design			
Thomé et al, 2021[33]	Neodent	Zr	Macrorough
Janner et al, 2018[25]	Institut Straumann	Zr	Microrough/sandblasted and acid-etched (hydrofluoric acid; ZLA)
Thoma et al, 2019[28]	Hexalobe w/ modified surface, AXIS Biodental	Zr	Hydroxyapatite coating
	Hexalobe, AXIS Biodental	Zr	Moderately rough
AlFarraj et al, 2018[39]	Medical grade Zr, Jansen Machining Technology	Zr	–
	Medical-grade Zr, Jansen Machining Technology	Zr (HA)	Hydroxyapatite coating
Chappuis et al, 2016[35]	Yttria-stabilized Zr with 5% yttria/Zerafil-TZP, Dentalpoint	TZP	Fine granular surface
	Alumina-toughened Zr with 4% yttria and 20% alumina/Zerafil-ATZ, Dentalpoint	ATZ	Fine granular surface
Park et al, 2013[41]	Zr implant created using the PIM technique with an untreated mold manufactured according to a proprietary process of CetaTech	Zr	–
	Zr 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[38]	E grade 3 mol Y-TZP, Toso	Zr	–
	E grade 3 mol Y-TZP, Toso	FS-Zr	Fusion-sputtering surface treatment
Kohal et al, 2013[37]	VITA Zahnfabrik	TZP-proc	Sandblasted with Al_2O_3 and acid-etched with hydrofluoric acid, nitric acid, and sulfuric acid
	VITA Zahnfabrik	TZP-A-m	Turned by machining
Mihatovic et al, 2017[30]	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[36]	Institute for Bioprocessing and Analytical Measurement Techniques	Y-TZP	Sandblasted
One- and two-piece designs			
Thoma et al, 2015[27]	VITA clinical ceramic implant, VITA Zahnfabrik H. Rauter	Zr (one-piece)	–
	Ziraldent, Metoxit	Zr (one-piece)	Microporous
	BPI Biologisch Physikalische Implantate	Zr (two-piece)	Nanostructured/hydrophilic surface
Benic et al, 2017[26]	VITA clinical ceramic implant, VITA Zahnfabrik H. Rauter	ZrO_2 (one-piece) + DBBM	Sandblasted and acid-etched with hydrofluoric acid, and annealing
		ZrO_2 (one-piece) + DBBM collagen	
		ZrO_2 (one-piece) + DBBM block	

PIM = powder injection molding.

Table 3 Description of Ti Implants Investigated in the Included Studies

Study	Implant system	Material	Surface morphology/treatment
One-piece design			
Delgado-Ruiz et al, 2014[29]	blueSKY, Bredent	Ti (grade 4)	Sandblasted with alumina oxide and acid etched
Liñares et al, 2016[34]	Institut Straumann	Ti	SLActive
El Awadly et al, 2020[31]	I-Fix, Dentis	Ti	Moderately rough
Calvo-Guirado et al, 2015 (Dec)[40]	blueSKY, Bredent	Ti	Sandblasted and acid etched
	blueSKY; Bredent	Ti (melatonin)	Sandblasted, acid-etched, and supplemented with MLT 5% in solution
Calvo-Guirado et al, 2015 (Jun)[32]	blueSKY, Bredent	Ti	Sandblasted and acid etched
Two-piece design			
Thomé et al, 2021[33]	Alvim with NeoPoros surface, Neodent	Ti	Microroughness/NeoPorous
Janner et al, 2018[25]	Standard Plus Regular Neck, Institut Straumann	Ti (grade 4)	Sandblasted, acid etched
Thoma et al, 2019[28]	Camlog Screw-Line Promote plus, Camlog	Ti	–
AlFarraj et al, 2018[39]	cpTi, Jansen Machining Technology	cpTi	–
	cpTi, Jansen Machining Technology	cpTi (HA)	Hydroxyapatite coating
Chappuis et al, 2016[35]	cpTi grade 4, TST Thommen Medical	cpTi (grade 4)	Microroughness
Park et al, 2013[41]	Machined-surface TI implant, Chaorum	Ti	–
Salem et al, 2013[38]	SLA, Tapered SP MTX, Zimmer Dental	Ti	Sandblasted and acid etched
Kohal et al, 2013[37]	TiUnite, Nobel Biocare	TiUnite	Roughened by electrochemical anodization
	TiUnite, Nobel Biocare	Ti-m	Turned by machining
Mihatovic et al, 2017[30]	Tissue Level, Standard, Institute Straumann	Ti	Sandblasted with grits size of 0.25–0.5 mm
Mueller et al, 2013[36]	Institute for Bioprocessing and Analytical Measurement Techniques	cpTi	Sandblasted and acid etched
One- and two-piece designs			
Thoma et al, 2015[27]	Straumann Tissue Level, Institut Straumann	Ti (grade 4, two-piece)	Sandblasted, acid etched
Benic et al, 2017[26]	Astra Tech OsseoSpeed S, Dentsply Sirona	Ti (grade 4, two-piece)	–

Table 4 Detailed Data on Outcomes of Included Studies

Study	Histomorphometric follow-up (mo)	Zr surface morphology/ treatment	Ti surface morphology/ treatment	Zr mean %BIC	Ti mean %BIC
One-piece design					
Delgado-Ruiz et al, 2014[29]	3	Sandblasted with alumina oxide particles Sandblasted with alumina oxide particles, treated with femtosecond laser pulses	Sandblasted with alumina oxide and acid etched 78 ± 5	48 ± 3	57 ± 6
Liñares et al, 2016[34]	2	ZLA surface	SLActive	86.24 ± 9.71	83.99 ± 3.61
El Awadly et al, 2020[31]	3	– Sandblasted	Moderately rough 51.1 ± 7.3	30.9 ± 12.7	54.0 ± 5.4
Calvo-Guirado et al, 2015 (Dec)[40]	0.25	Sandblasted	Sandblasted and acid etched	22.8 ± 1.5 (0.25 mo) 37.5 ± 2.1 (1 mo)	25.4 ± 1.2 (0.25 mo) 38.4 ± 1.8 (1 mo)
	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 (0.25 mo) 47.5 ± 2.2 (1 mo)	29.7 ± 2.4 (0.25 mo) 39.2 ± 2.5 (1 mo)
Calvo-Guirado et al, 2015 (Jun)[32]	1 3	Modified by femtosecond laser	Sandblasted and acid etched	44.68 ± 17.66 (1 mo) 47.94 ± 16.15 (3 mo)	51.36 ± 12.03 (1 mo) 61.73 ± 16.27 (3 mo)
Two-piece design					
Thomé et al, 2021[33]	2	Macroroughness	Microroughness/ NeoPorous	77.8 ± 6.9	80.7 ± 6.9
Janner et al, 2018[25]	1 3.5	Microrough/sandblasted and acid etched (hydrofluoric acid; ZLA)	Sandblasted and acid etched 71.15 ± 7.03	75.58 ± 6.26 69.76 ± 8.07	76.88 ± 2.84
Thoma et al, 2019[28]	0.5 8	Hydroxyapatite coating Moderately rough	– 35.77 ± 8.14 (0.5 mo) 75.34 ± 17.95 (8 mo)	46.9 ± 12.14 (0.5 mo) 81.48 ± 14.26 (8 mo)	46.05 ± 11.78 (0.5 mo) 74.65 ± 10.76 (8 mo)
AlFarraj et al, 2018[39]	2	– Hydroxyapatite coating	– Hydroxyapatite coating	45.1 ± 14.8 60.3 ± 17.1	45.5 ± 13.1 59.8 ± 16.4
Chappuis et al, 2016[35]	1 2	Fine granular surface	Microroughness 70.00 (1 mo) 57.04 (2 mo)	64.37 (1 mo) 60.88 (2 mo)	82.30 (1 mo) 79.86 (2 mo)
Park et al, 2013[41]	1	–	– 64.42 ± 11.45	61.63 ± 12.39	42.54 ± 10.26
Salem et al, 2013[38]	1 2 3	– Fusion-sputtering surface treatment	Sandblasted and acid etched 69.66 ± 3.46 (1 mo) 88.03 ± 2.94 (2 mo) 89.09 ± 2.81 (3 mo)	56.94 ± 2.91 (1 mo) 70.36 ± 2.88 (2 mo) 74.76 ± 3.85 (3 mo)	62.83 ± 1.97 (1 mo) 82.94 ± 2.79 (2 mo) 86.77 ± 3.09 (3 mo)
Kohal et al, 2013[37]	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 (0.5 mo) 33.5 ± 4.1 (1 mo)	36.2 ±12.9 (0.5 m) // 56.1 ± 15.8 (1 mo)
	1	Turned by machining	Turned by machining	30.9 ± 10.1 (0.5 m) 46.6 ± 13.89 (1 mo)	23.2 ± 6.3 (0.5 mo) 39.4 ± 3.9 (1 mo)

Table 4 Detailed Data on Outcomes of Included Studies (cont)

Study	Histomorphometric follow-up (mo)	Zr surface morphology/treatment	Ti surface morphology/ treatment	Zr mean %BIC	Ti mean %BIC
Mihatovic et al, 2017[30]	0.033	Sandblasted with grit size of 0.05 µm	Sandblasted with grits of 0.25–0.5 mm 30.03 ± 9.97 (0.033 mo) 44.46 ± 22.95 (0.5 mo) 39.01 ± 0.0 (2.5 mo)	25.06 ± 13.65 (0.033 mo) 42.39 ± 23.44 (0.5 mo) 49.71 ± 33.65 (2.5 mo)	42.26 ± 10.5 (0.033 mo) 62.19 ± 10.71 (0.5 mo) 58.59 ± 17.24 (2.5 mo)
	0.5	Sandblasted with grit size of 0.11 µm			
	2.5	Sandblasted with grit size of 0.25 µm	28.97 ± 9.52 (0.033 mo) 61.25 ± 17.71 (0.5 mo) 69.57 ± 16.27 (2.5 mo)		
Mueller et al, 2013[36]	2 4	Sandblasted	Sandblasted and acid etched	73.9 ± 19.0 (2 mo) 72.1 ± 20.0 (4 mo)	57.4 ±19.0 (2 mo) 70.9 ± 19.0 (4 mo)
One- and two-piece designs					
Thoma et al, 2015[27]	12	– Microporous Nanostructured/hydrophilic surface	Sandblasted and acid etched 78.58 ± 17.26 84.17 ± 25.07	87.71 ± 25.07	87.85 ± 13.59
Benic et al, 2017[26]	3	Sandblasted, acid etched with hydrofluoric acid, and annealing	– 69 ± 22 77 ± 30	70 ± 19	66 ± 27

critical for assessing the progress of osseointegration, as it is advantageous if an implant's osseointegration improves with time.

A total of 370 Ti implants and 537 Zr implants were evaluated. The materials of the Zr implants included zirconium, tetragonal zirconia polycrystal (TZP), alumina-toughened zirconia (ATZ), yttrium-stabilized tetragonal zirconia (Y-TZP), and zirconium dioxide (ZrO_2). The materials of the titanium implants were commercially pure Ti (cpTi) and cpTi grade 4.

Osseointegration Rates

Osseointegration rates were compared in all investigations using %BIC. The rates were similar between Zr and Ti implants. The average BIC for Zr was 55.51% (17.6% to 89.09%) and for Ti was 58.50% (23.2% to 87.85%).

One- and two-piece Zr had a similar osseointegration rate to one- and two-piece Ti. In all studies except Janner et al,[25] 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, making any kind of statistical analysis unfeasible. There was no statistical difference between studies at 2 months ($P = .672$), but significant differences were found at both 1 and 3 months ($P < .001$; Appendix Fig 1).

Studies in Dogs

Dogs were used as animal models to investigate osseointegration rates in eight studies.[25–32] Seven studies used the mandible as the location of implantation; only Benic et al[26] placed implants in the maxilla. Thoma et al[27] reported the highest osseointegration rate of Ti (87.85 ± 13.59%) and Zi (87.71% ± 25.07%) implants among these studies.

Studies in Minipigs

Four studies used minipigs as animal models.[33–36] Implants were placed in the mandible, maxilla, and skull. Liñares et al[34] reported the highest osseointegration of Zr (86.24% ± 9.71%) and Ti (83.99% ± 3.61%) implants among these studies.

Studies in Rats

Kohal et al[37] was the only investigation to use rats as animal models. The implantation location was the femur, and the histomorphometric analysis was at 0.5 months and 1 month. The highest %BIC of the Zr implants investigated was 46.6% ± 13.89% (1 month) for a Zr implant (VITA Zahnfabrik) turned by machining. The greatest osseointegration rate of the Ti implants was 56.1% ± 15.8% (1 month) for a roughened electrochemical anodization implant (TiUnite, Nobel Biocare).

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
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
Liñares et al, 2016	1	1	2	0	2	2	2	2	1	2	1	2	2	0	1	2	1	1	2	1
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
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
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
Thomé et al, 2021	1	1	2	0	2	2	2	2	1	2	0	2	2	1	2	2	2	1	2	2
Janner et al, 2018	1	1	2	0	2	2	2	1	1	1	1	1	2	1	2	2	2	2	2	2
Thoma et al, 2019	1	1	2	0	2	2	2	1	1	2	1	2	2	1	1	2	2	2	2	2
AlFarraj et el, 2018	1	2	2	0	1	2	1	1	1	2	1	1	2	1	1	2	2	2	2	0
Chappuis et al, 2016	1	2	2	0	2	2	2	1	0	1	1	1	2	1	1	2	1	1	2	2
Park et al, 2013	1	1	2	0	1	2	2	1	2	2	0	1	2	1	1	2	1	1	2	1
Salem et al, 2013	1	1	2	0	1	1	1	1	2	1	1	1	2	1	1	2	2	2	2	0
Kohal et al, 2013	1	1	2	0	2	1	2	0	0	1	1	1	2	1	2	2	2	2	2	1
Mihatovic et al, 2017	1	1	1	0	1	2	2	1	1	2	1	1	2	1	2	2	2	1	1	2
Mueller et al, 2013	1	1	1	0	2	2	1	2	1	1	1	1	2	0	1	2	1	1	1	0
Thoma et al, 2015	1	1	1	0	2	2	2	1	1	1	1	1	2	1	2	2	2	1	2	2
Benic et al, 2017	1	1	2	0	1	2	2	2	2	1	1	2	2	1	2	2	1	1	1	2

Fig 2 Quality assessment of included studies.

Studies in Rabbits

Four studies utilized rabbits as animal models.[38–41] Implants were placed in the tibia and the femur. Salem et al[38] reported the highest osseointegration rate for Zr and Ti implants at 89.09% ± 2.81% and 86.77% ± 3.09%, respectively.

Quality Assessment and Statistical Results

The quality assessment of the included studies is presented in Fig 2, and the categories and grading used to assess the quality of the experimental animal studies are described in Appendix Table 3. All 17 studies evaluated had accurate and concise titles. Only 3 studies had clearly accurate abstracts that included a summary of the background (score = 2), and the remaining 14 lacked only that topic (score = 1). Only 3 articles received a score of 1 for the background developed in the introduction due to the absence of information. All other articles had clearly proper introductions (score = 2). Regarding the objectives in the introduction, all studies had clear goals (score 0).

Regarding methods, 7 articles (41.17%) had an incomplete ethical statement (score = 1, possibly accurate), and the rest described 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 regard to the experimental procedure, 3 studies (17.64%) lacked all the precise details of the procedure (score = 1), but the others had a detailed description of the procedure (score = 2). Five articles (29.41%) provided adequate information regarding the experimental animals, 11 studies (64.71%) reported possibly accurate information, and only 1 study[40] (5.88%) included insufficient data. Concerning 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 details on 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%) did not make an allocation. The experimental outcomes were well defined in 5 articles (29.41%), whereas the others were unclear or incomplete (score = 1). All 17 studies provided clear statistical methods.

Regarding the results, 12 articles (70.59%) provided baseline data characteristics and health status of the animals, whereas the rest did not provide sufficient information, especially regarding the health of the animals. Outcomes were clearly described in all 17 studies. Adverse events were adequately reported in 10 studies

(58.82%) and possibly accurately reported in the other studies, where the presence or absence of adverse events was not reported. Regarding 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 explicit in 13 studies (76.47%), whereas others had possibly real 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%).

A meta-analysis (Appendix Fig 1) was undertaken for data from the 1-, 2-, and 3-month postsurgery follow-ups to analyze osseointegration. The results for 1 month showed high heterogeneity among the studies (I^2 = 95.78%), with significant results found ($P < .001$). The regression test indicated funnel plot asymmetry ($P = .0016$; Fig 3), but not the rank correlation test ($P = .8406$). Moreover, the estimated average standardized mean difference was 0.2263 (95% CI: 0.0212 to 0.4313). Therefore, the average outcome differed significantly ($P = .0306$).

After 2 months, only three studies and four groups were analyzed. There was no heterogeneity among them (I^2 = 0%, $P = .672$). The estimated standardized mean difference was –0.0967 (95% CI: –0.5300 to 0.3365). Therefore, the average outcome did not differ significantly ($P = .6617$). Neither the rank correlation nor regression test indicated any funnel plot asymmetry ($P = .7500$ and $P = .2918$, respectively).

At 3 months, the studies also had high heterogeneity (I^2 = 91.61%), with significant statistical results found ($P < .001$). Neither the rank correlation nor regression test indicated any funnel plot asymmetry ($P = 1.0000$ and $P = 0.2771$, respectively; see Fig 3). The estimated standardized mean difference was –0.2939 (95% CI: –2.7627 to –0.0854). However, the average outcome differed significantly ($P = .0057$).

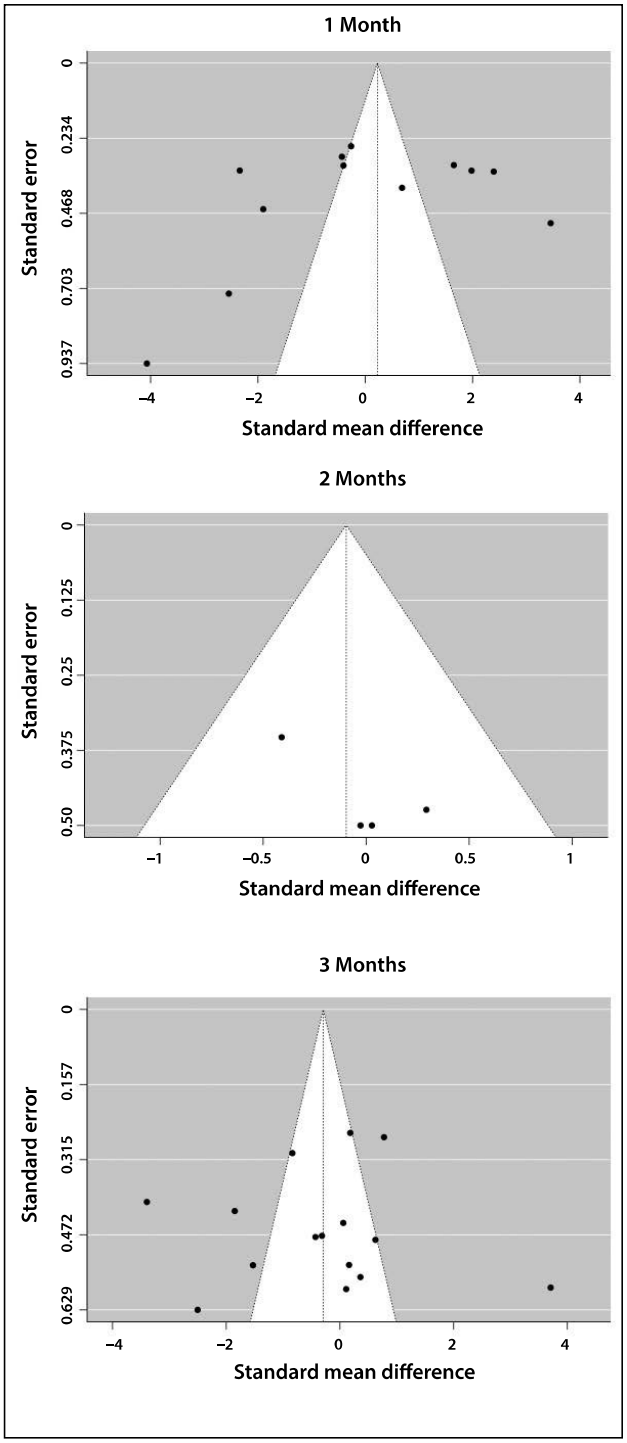

Fig 3 Funnel plots at 1, 2, and 3 months.

DISCUSSION

Ti implants, the gold standard material for dental implants, offer a reasonable survival rate and excellent strength, biocompatibility, and osseointegration. However, they can produce unsatisfactory results in esthetic rehabilitation. As a result, there has been a rise in research on Zr implants due to their promising characteristics, such as their ivory color, low elasticity modulus, high flexural strength, toughness, radiopacity, and biocompatibility, low plaque affinity, good osseointegration, and satisfactory survival rate.[11]

One of the most critical factors determining the lifespan of a dental implant is osseointegration. As a result, this systematic review examined the possible recommendations for using Zr implants beyond esthetic-driven scenarios by comparing the osseointegration rates between Zr and Ti implants using histologic analysis.

Histologic Osseointegration Levels

Research has demonstrated that dental implant materials do not significantly influence the osseointegration rates of implants.[42–44] Indeed, a recent systematic review of animal studies[45] reported similar results for mean %BIC compared to the present study (59.1% for Ti implants and 55.9% for Zr implants). In addition, Pieralli et al[42] reported a mean %BIC of 60.70% for Ti implants and 57.23% for Zr implants (a reduced %BIC of –3.47%).

Another study comparing only implant material reported that Ti showed better osseointegration than Zr. On the other hand, after surface treatment, Zr displayed a similar rate of osseointegration compared to Ti. Thus, surface roughness (Ra) might be a determinant factor for better osseointegration.[18] Moreover, because the variation in surface roughness has a more considerable influence on osseointegration rates than the material itself, the surface treatments should be comparable when analyzing the implant's primary body material (Zr and Ti).[46] Most studies in the present systematic review investigated different types of implant surfaces to research their impact on osseointegration. However, when comparing Zr and Ti implants with similar surface treatments, there was no significant difference in %BIC. For instance, AlFarraj et al[39] reported an osseointegration rate of 60.3% ± 17.1% for Zr implants and 59.8% ± 16.4% for Ti implants comparing the same surface treatment (hydroxyapatite coating) after 2 months.

Many surface features, such as topography, wettability, and coating, can influence early osseointegration. According to previous research, isotropic (irregularities without specific direction) and moderately rough surfaces (1 to 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 adhesion of the first proteins that contact the implant surface.[47–50]

Salem et al[38] showed the highest mean %BIC result for Zr implants of 89.09% at 3 months. This Zr implant (E grade 3 mol Y-TZP, Toso) received fusion-sputtering surface treatment resulting in a microrough surface that improved bone apposition at the bone-to-implant interface. A sprayed suspension of zirconia mixture made of 5 g ultrafine zirconia powder (1 to 5 µm) and 10 mL ethyl alcohol (70%) was used for this surface treatment. Scanning electron microscopy (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 implant's outer surface. Although this surface treatment is new and requires additional research, particularly findings on its long-term performance, it has the potential to be an ideal surface treatment for implants.[38,51]

Thoma et al[27] reported the highest mean osseointegration rate of Ti implants of 87.85% at 12 months. 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 micropits emerge.[52] This surface roughening approach is typically applied in the implant fabrication industry because it has been shown to contribute to a higher %BIC (50% to 60%) compared to, for example, Ti plasma spray treatment (30% to 40%).[52,53]

Furthermore, the osseointegration rates of implants rose with time in most of the included studies. This is related to the bone remodulation process during the shift to secondary stability.[7] In the majority of included studies, Ti implants exhibited higher osseointegration rates throughout the early healing phase; however, in most cases, there was no significant difference in %BIC between Ti and Zr implants throughout this period.

Another aspect to consider is the effect of implant loading. Most of the included studies did not investigate osseointegration in loaded implants. Delgado-Ruiz et al[29] investigated the behavior of Zr implants with immediate loading and concluded that %BIC was higher in immediately loaded implants in both Zr and Ti groups.

Finally, although the present study compared the osseointegration of two materials, additional elements that have a massive effect on osseointegration must not be overlooked. Surface properties impact primary stability and, more particularly, the lifetime of dental implants. Additionally, the implant design is the most important aspect influencing primary stability and the implant's capacity to tolerate loading following osseointegration.[54]

Animal Models

Preclinical in vivo research is critical in implantology research for determining the biologic relevance, biofunctionality, biocompatibility, and clinical effectiveness of an implant.[44] 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 model's age, and the site's blood supply, which differ by species, must all be evaluated.[44]

The animal models most often used in implantology are rats, rabbits, dogs, pigs, sheep, and goats.[44] No species meets all the criteria for an ideal model. Each model, however, can be recommended for use in specific investigations. The rabbit is one of the most used

models; however, it has the lowest resemblance to human bone. While the pig resembles human bone, issues may arise because of its size and ease of handling. In this regard, the dog and sheep/goat appear more promising as animal models for investigating bone implant materials.[55] In fact, dogs were the most commonly used animal model in the studies included in the present review (n = 8).

Finally, standardizing evaluation metrics is problematic due to the variety of animal models that might be used in implant research. Indeed, there was some disparity in the present findings between investigations using different animal models. Therefore, to properly analyze and compare research outcomes, attempts to standardize preclinical animal experiments are necessary.[42] Furthermore, even though there are just a few systematic reviews of preclinical animal studies, they may help enhance the quality of future animal-based studies and offer an evidence-based transition between preclinical and clinical studies.[42]

Study Limitations

The present systematic review found only preclinical studies, as these are the most effective way to assess osseointegration of implants through histologic analysis. The studies included compared osseointegration rates of Zr implants to Ti implants, but there was a lack of standardization, especially when it came to period of analysis. Thereby, as a result of the preclinical nature of these findings, all data and results must be critically verified. Moreover, another limitation of the current systematic review was that not all the included articles reported information about the surface treatment of the implant. This prevented appropriate comparison of osseointegration outcomes.

CONCLUSIONS

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

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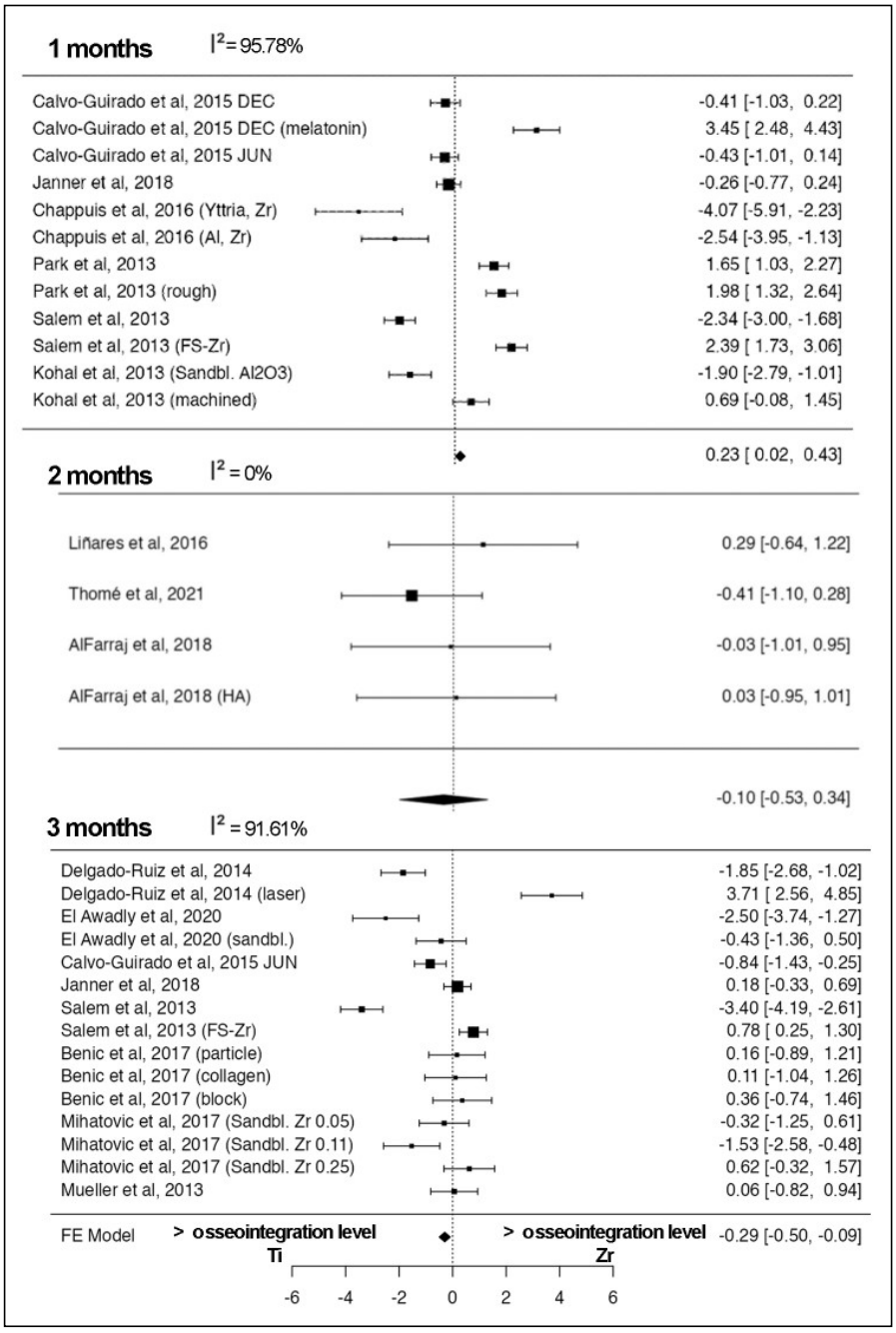
APPENDIX

Appendix Fig 1 Forest plots showing %BIC at 1, 2, and 3 months.



Appendix Table 1 PICO Research Question

Patient/population	Subject receiving dental implant
Intervention	Zirconia implants
Comparison	Titanium implants
Outcome	Histologic analysis, survival rate, Osseointegration, bone loss

Appendix Table 2 Search Strategies

	PubMed/MEDLINE and 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: Histologic 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)	

Appendix Table 3 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 (ie, allocation concealment, randomization, blinding)	0 = clearly inaccurate 1 = possibly accurate 2 = clearly accurate
7	Methods Experimental procedure: precise details (ie, 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 (ie, 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

Appendix Table 3 Categories and Grading Used to Assess the Quality of the Experimental Animal Studies (cont)

Item	Description	Grade
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 (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

Appendix Table 4 Reasons for exclusion of studies after full-text screening

Author/year	Reason for exclusion
Kim et al, 2021	Insufficient data
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
Gredes et al, 2014	Insufficient data
Aboushelib et al, 2013	Insufficient data
Igarashi et al, 2018	Insufficient data