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ORIGINAL ARTICLE

Peri-Implant bone response around porous-surface dental implants: A preclinical meta-analysis

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KEYWORDS

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Abstract *Introduction:* This *meta*-analysis of relevant animal studies was conducted to assess whether the use of porous-surface implants improves osseointegration compared to the use of non-porous-surface implants.

Material and methods: An electronic search of PubMed (MEDLINE) resulted in the selection of ten animal studies (out of 865 publications) for characterization and quality assessment. Risk of bias assessment indicated poor reporting for the majority of studies. The results for bone-implant contact (BIC%) and peri-implant bone formation (BF%) were extracted from the eligible studies and used for the meta-analysis. Data for porous-surface implants were compared to those for non-porous-surface implants, which were considered as the controls.

Results: The random-effects meta-analysis showed that the use of porous-surface implants did not significantly increase overall BIC% (mean difference or MD: 3.63%; 95% confidence interval or 95% CI: −1.66 to 8.91; p = 0.18), whereas it significantly increased overall BF% (MD: 5.43%; CI: 2.20 to 8.67; p = 0.001), as compared to the controls.

Conclusion: Porous-surface implants promote osseointegration with increase in BF%. However, their use shows no significant effect on BIC%. Further preclinical and clinical investigations are required to find conclusive evidence on the effect of porous-surface implants.

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1. Introduction

Today, dental implants have become a reliable treatment option for oral rehabilitation of patients with missing teeth (Smeets et al., 2016). Dental implants are superior to conventional prosthetics as they have better esthetics, provide greater mastication ability, and result in higher patient satisfaction. In fact, the biological integration of dental implants in the jaw-

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bone (i.e., osseointegration, as defined by Brånemark in 1965) is considered to be a fundamental reason for their long-term success (Le Guehennec et al., 2007). However, implant osseointegration can be affected by several factors such as poor bone quality and quantity, which depends on the patient's medical condition (Kate et al., 2016; Mohajerani et al., 2017). In principle, the inherent properties of dental implants can promote natural biological processes such as bone formation during early osseointegration (Dohan Ehrenfest et al., 2010). In this way, the surface properties of the implant can affect the quality of bone-implant healing (Huang et al., 2015; Liu et al., 2017; Cheng et al., 2018). Therefore, researchers have attempted to develop several surface modifications that could promote osseointegration.

Implant surface modification aims to modify the surface topography as well as surface area of the implant to promote cell proliferation and growth in the local environment (i.e., favor more bone formation on the implant surfaces) (Jemat et al., 2015; Smeets et al., 2016; Wirth et al., 2017). However, most of the current surface modifications facilitate only superficial interactions between the recipient bone and the outer surface layer of titanium implants (Jemat et al., 2015). Therefore, several alternative approaches have been proposed to create porous-structured implants (Wally et al., 2015) such as the new dental implant system with large porous structure in the surface topography (i.e., Trabecular Metal Zimmer® Implant System) (Wally et al., 2015). High porosity of the implant surface is expected to increase the *peri*-implant response. Hypothetically, a surface topography with large porous structures can provide several biological advantages for bone-implant integration over other implant surface designs (Bandyopadhyay et al., 2010; Wazen et al., 2010; Fraser et al., 2019). Several investigators have examined the effect of porous-surface design on implant osseointegration in numerous preclinical studies (Burgos et al., 2008; de Vasconcellos et al., 2010; Baril et al., 2011; Guo et al., 2013; Kim et al., 2013). However, due to considerable variations in study protocols there is no consensus regarding the research findings. Additionally, the exact biological mechanisms that result in improved *peri*-implant bone response around porous-surface implants are not completely understood.

Thus, we conducted a preclinical *meta*-analysis to determine the effect of porous-surface implants versus conventional solid implants on implant osseointegration. Quantitative measures of the implant characteristics including histomorphometrical bone-implant contact (BIC%) and *peri*-implant bone formation (BF%) were selected as outcomes in the *meta*-analysis.

2. Material and methods

2.1. Search strategy

An electronic search of PubMed (MEDLINE) was performed using previously described methods (Leenaars et al., 2012). The search was initiated in February 2019 and then updated every three months, with the last update in July 2020. The PubMed database was searched for animal studies using search terms related to "porous-surface implants" and "osseointegration." Thesaurus and free text terms were also identified, as previously mentioned (Hooijmans et al., 2010).

Additional manual searches were performed by screening the bibliographies from retrieved reviews and publications that were relevant and adding free-text words from titles or abstracts.

2.2. Study selection

All studies retrieved from the search were imported into a bibliographic referencing software program (EndNote_ X9, www.endnote.com), and duplicate references were identified and removed. First, the relevant titles and abstracts were screened and subsequently excluded if: (1) the title was clearly not relevant to implant osseointegration, (2) it was specifically mentioned in the title/abstract that in vitro studies were performed, (3) it was a review article, (4) it was a human clinical study, or (5) it was a non-English language publication. The exact reasons for exclusion were recorded.

Second, articles were retrieved in full text and assessed if they fulfilled all inclusion criteria: (1) original animal research, (2) comparing porous-surface implants with non-porous-surface implants, (3) implantation sites and time periods were mentioned, and (4) English language was used for publication.

2.3. Data extraction and study characteristics

The data extraction process was conducted using a data extraction sheet that specified relevant study details including author, year of publication, study design, animal model (species, sex, age, weight, number of animals, and medical condition), information related to implantation procedures (number of implants, anatomical site, and healing time), and reported implant outcomes that quantified the *peri*-implant bone response including BIC% and BF%.

2.4. Assessment of reporting quality and risk of bias

The Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) risk of bias tool (Hooijmans et al., 2014) was used to assess the quality of reporting and risk of bias for the included studies. None of the studies were excluded because of this quality appraisal. For reporting quality, "randomization" and "blinded assessment" were used as indicators; the "Yes" score meant that these indicators had been reported, whereas the "No" score meant that the indicators had not been reported. Moreover, to determine the risk of bias, the following components were assessed: (1) selection bias, (2) performance bias, (3) detection bias, and (4) attrition bias. In this assessment, "Yes" indicated low risk of bias for studies, "No" indicated high risk of bias, and "Unclear" indicated an unclear risk of bias.

2.5. Outcome data extraction and quantitative data synthesis (meta-analysis)

Data for the study groups (experimental and control) were extracted for all outcome variables such as mean, standard deviation (SD), and number of implants. The experimental groups consisted of animals that had received the porous-surface implants, whereas the control groups consisted of animals with non-porous-surface implants.

When findings of an included study were presented in graphs, the ImageJ (1.46r; National Institutes of Health, Bethesda, MD) software was used to measure the mean and SD.

Meta-analysis was restricted to studies containing implant data comparisons between the experimental and control groups.

Using the two outcome measures (BIC% and BF%), a *meta*-analysis was performed to examine the overall effect of using porous-surface implants on osseointegration compared to those used in the control group (implants without porous-surface).

Review Manager 5 software (RevMan 5, http://tech.cochrane.org/revman) provided by the Cochrane Collaboration (RevMan 5) was used to perform the *meta*-analysis. Heterogeneity was evaluated using the I^2 metric and random-effects modeling was used for the *meta*-analysis. The mean difference (MD) with corresponding 95% confidence interval (CI) was used to indicate effect size. Differences between groups were considered statistically significant when there was no overlap between the CIs (Training, 2011). Finally, funnel plots were used to assess publication bias for the overall outcome of each study.

3. Results

3.1. Selected studies

A flowchart for the selection of studies is shown in Fig. 1. The electronic search identified a total of 865 studies in PubMed. Screening of titles and abstracts reduced the list to 142 publications. Finally, only ten articles were selected for evaluation, data extraction, and interpretation.

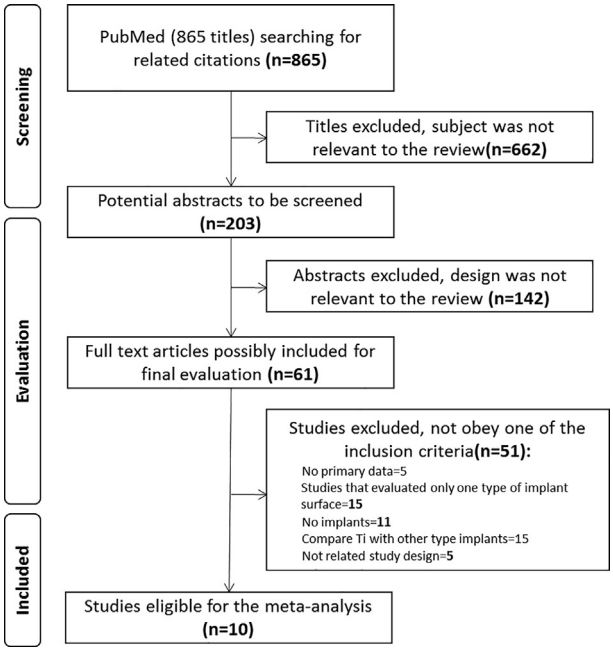

Fig. 1 Flow-chart of the systematic search of literature and the process of study selection according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis).

3.2. Characteristics of included studies (Table 1)

Different animal species including small (rabbits in two studies) and large animal models (pigs in one study, dogs in three studies, goats in two studies, and sheep in two studies) were used in the eligible studies. All animals used in the studies were healthy. Sample sizes ranged from 3 to 48. Substantial variations were observed among the implantation protocols used in the studies. Several anatomical bone sites were assigned to place implants (i.e., tibia, femur, iliac crest, lumber, mandible, and frontal skull). In addition, the implantation period differed among the studies. The shortest period of implantation was two weeks, whereas the maximum implantation time was 12 months. In the majority of studies, implant healing time ranged from two weeks to six months. (See Table 1)

3.3. Methodological quality of studies

The overall results of the reporting quality as well as risk of bias (selection, performance, detection, and attrition biases) assessments are presented in Fig. 2A. The articles did not mention any blinding at any level of the experiments. On the other hand, randomization was reported in approximately five articles. However, none of the included articles provided details on the method of randomization. Therefore, we were not able to assess the adequacy of randomization. The majority of the included studies had "unclear risk" of selection bias, as there was no information available regarding the sequence of allocation and details of concealment. On the other hand, eight of the included articles were marked as "Yes" for baseline similarity. Three of the included articles provided information regarding performance bias (i.e., animals were randomly housed). However, it was difficult to determine performance bias in the remaining studies due to lack of information regarding random housing of animals during the experiment and/or whether the caregivers/investigators were blinded from the experimental design. One article had a low risk of detection bias because the investigators randomly selected the animals for the outcome assessment. Finally, we found complete outcome data in > 30% of reports, which were determined to have low risk of attrition bias. However, any missing data were difficult to determine for the remaining studies.

3.4. Quantitative data synthesis (meta-analysis)

All ten studies were selected for the review and were also included in the *meta*-analysis. More than one comparison (experimental vs. control) could be retrieved from the eligible studies wherein one or more implant outcomes (BIC% and BF%) were reported. An overview of the *meta*-analysis and results (MD; 95% CI; number of comparisons, and number of implants) has been given in Table 2 and Figs. 3 and 4 (forest plots).

Overall, the *meta*-analysis indicated a non-significant improvement in implant osseointegration adjacent to porous-surface implants compared to controls, as quantified by histomorphometrical BIC% (MD: 3.63%; CI: −1.66 to 8.91; $p = 0.18$; Fig. 3).

On the other hand, the *meta*-analysis indicated a significant improvement in implant osseointegration adjacent to porous-surface implants compared to controls, as quantified by histo-

Table 1 Characteristics of studies included in review.

Author	Year	Animal Model/ No.	Site	No. of Implant	Implant Design (Test \Control)	Implantation Time	BIC %	BF%
Alshehri et al.	2019	Goat 6	Iliac Crest	12	Porous titanium implants (t)	7 weeks		9.89 ± 3.69 (t)
					Solid titanium implants (c)			8.63 ±3.93 (c)
Assad et al.	2003	Dorset sheep 16	Lumbar Spine	32	Porous titanium-nickel implant (t)	3 months	10.9 ± 10 (t) 3.6 ± 1.5 (c)	21.4 ± 6 (t) 22.7 ± 4 (c)
						6 months	25.3 ± 10 (t) 1.1 ± 1 (c)	33 ± 6 (t) 21.3 ± 4 (c)
					Nonporous commercial Ti (c)	12 months	24.2 ± 10 (t) 5.1 ± 5 (c)	37.6 ± 5 (t) 25.4 ± 1 (c)
Barrere et al.	2003	Goat 14	Femoral Diaphysis	41	Porous tantalum (t)	6 weeks	1 ± 1 (t) 2 ± 4 (c)	
					Dense titanium (c)	12 weeks	7 ± 7 (t) 8 ± 12 (c)	
						24 weeks	9 ± 3 (t) 21 ± 14 (c)	
Brentel et al.	2006	Rabbit 7	Tibiae	42	Porous-surface implants (t)	4 weeks	79.69 ± 1 (t) 65.05 ± 1.23 (c)	
					Rough-surface implants (c)			
Fraser et al.	2019	Rabbit 48	Tibiae	96	Porous tantalum implant(t)	4weeks	34.6 ±13.8 (t)	37.1 ± 8.4 (t)
					Solid titanium implant (c)		14.3±4.9 (c)	34.3 ± 10.4 (c)
						8 weeks	38±9.3(t) 20±6.3 (c)	36.2 ± 7 (t) 37.1 ± 7.9 (c)
						12 weeks	50.8±11.2 (t) 30.1±8.8 (c)	39.1 ± 9.3(t) 36.7 ± 6.1 (c)
Kim et al.	2013	Dogs 8	Mandible	48	A highly Porous tantalum (t)	2 weeks	35.9 ± 14.2(t) 33.3±16.5(c)	
						4 weeks	36.3 ± 17.5 (t) 43.3 ±24.5 (c)	
					Threaded, tapered dental implant (c)	8 weeks	48.8 ± 10.6 (t) 42.2 ±10.5 (c)	
						12 weeks	47.2 ± 6 (t) 43.2 ±12.6 (c)	
Lee et al.	2015	Dogs 6	Mandible	48	Trabecular metal implants (t)	2 weeks	33.74 ± 9.4 (t) 33.15 ± 13.2 (c)	28.8 ± 9.88 (t) 33.53 ± 8.62 (c)
					Tapered screw- implants (c)	4 weeks	25.35 ± 4.86 (t) 25.35 ± 8.68 (c)	32.43 ± 2.84 (t) 25.61 ± 7.5 (c)
						12 weeks	63.98 ± 10.66 (t) 73.13 ±14.9 (c)	55.58 ± 10.73 (t) 54.72 ± 8.36 (c)
Lee et al.	2018	Dogs 8	Mandible	64	Highly porous implants (t)	2 weeks		32 ±12 (t) 15 ± 10 (c)
					Threads tapered screw-vent® dental implants (c)	4 weeks		27 ± 13 (t) 14 ± 8 (c)
						8 weeks		37 ± 13 (t) 25 ± 14 (c)
						12 weeks		48 ± 15 (t) 25 ± 14 (c)
Palmquist et al.	2013	Sheep 3	Femur	12	Porous cylindrical Implants (t)	26 weeks	63 ± 6 (t) 60 ± 9 (c)	90 ± 5 (t) 88 ± 5 (c)
					Solid machined cylindrical			

Table 1 (*continued*)

Author	Year	Animal Model/ No.	Site	No. of Implant	Implant Design (Test \Control)	Implantation Time	BIC %	BF%
					implants (c)			
Ponader et al.	2010	Pigs 15	Frontal Skull	30	Porous titanium implants (t)	14 days	0.47 ± 0.47 (t) 29.27 ± 11.23 (c)	
						30 days	4.14 ± 4.14 (t) 18.78 ± 9.74 (c)	
					Smooth compact titanium (c)	60 days	5.96± 1.36 (t) 8.98 ± 2.89 (c)	

t test group; c control group.

morphometrical BF% (MD: 5.43%; CI: 2.20 to 8.67; p = 0.001; Fig. 4).

However, not all studies/comparisons showed the same direction of effect. As shown in Table 2, 348 implants were used in 21 comparisons to estimate the overall effect of porous-surface implants versus non-porous-surface implants on osseointegration based on the BIC%. Of these, six comparisons showed a positive effect, whereas four comparisons showed a negative effect, and 11 comparisons showed no effect (Table 2). For BF%, 264 implants were used in 15 comparisons (Table 2). Positive overall effects were observed in six comparisons, no comparison showed a negative effect, and nine comparisons showed no effect (Table 2).

3.5. Publication bias

As shown in Fig. 2B and C, the shapes of the funnel plots (for each main outcome variable) do not clearly indicate small study effects, which may be related to publication bias.

4. Discussion

This pre-clinical *meta*-analysis of relevant animal studies was conducted to investigate whether the use of porous-surface implants can significantly improve osseointegration compared to non-porous-surface implants. In recent years, the use of porous-surface implants to enhance osseointegration has been evaluated in several animal models. Pooling and analysis of the data from selected studies indicated that porous-surface implants may have a positive effect on BF% during osseointegration, compared to non-porous-surface implants. Similarly, there was a comparable effect on BIC%. However, variations in the animal models, study protocols, and follow-up times might influence study outcomes, which could explain the high heterogeneity (I^2 = 90%) in previous studies. These insights may be helpful in designing more robust research studies in the future.

Interestingly, the use of porous-surface implants showed a positive effect on BF% in six of the evaluated comparisons (Assad et al., 2003; Lee et al., 2015; Lee et al., 2018). For instance, Assad et al. and Lee et al. demonstrated that porous implant surfaces have a favorable effect on bone formation in comparison to the use of non-porous-surface implants. However, it should be emphasized that the remaining nine comparisons (Palmquist et al., 2013; Lee et al., 2015; Alshehri et al., 2019; Fraser et al., 2019) did not indicate any effect of porous-surface implants on BF%. For example, Al-Shehri et al. and Fraser et al. found no significant difference in bone formation at any time point between the test and control groups.

The use of porous-surface implants increased BIC% in six comparisons (Assad et al., 2003; Brentel et al., 2006; Fraser et al., 2019), whereas it decreased BIC% (negative effects) in 11 out of 21 comparisons (Barrere et al., 2003; Kim et al., 2013; Lee et al., 2015). In addition, four studies showed no effect of porous-surface implants on BIC% (Barrere et al., 2003; Ponader et al., 2010).

The negative effects on bone formation seen in these studies maybe attributable to several reasons. The current literature on bone-implant interfaces comprises studies that have used different methods, providing varying results, which makes their comparison difficult. Another reason is the use of the bone-to-implant contact assessment method. To date, the gold standard to assess the bone-implant interface is histomorphometrical analysis. Several histomorphometrical analysis methods such as microscopic magnification, software, and algorithms can play a critical role in BIC calculations, which might consequently lead to different results. Furthermore, after the sacrifice of animals, bone tissue must be instantly transferred to a specialized laboratory for pre-assessment preparation. Other types of pre-assessment preparations such as fixation methods used in research protocols, thin tissue preparation, and animal tissue fixation in formalin may influence the final results.

In addition, variation in the surface area (whole or part of the implant surface) of the implant that is studied can affect results. Other critical factors responsible for variation in bone-implant response reported in previous studies are material properties of the implant, different animal models, different anatomic locations of the implant placement as well as different healing times after implantation (i.e., ranging from one week to six months) (Kim et al., 2013; Palmquist et al., 2013; Lee et al., 2015).

Analytical methods to evaluate osseointegration via histological sections are commonly provided in dental implant literature. Although histomorphometrical quantification of BIC and BF only provides information based on two-dimensional (2D) histological sections from a 3D complex bone-implant structure, it is considered as the "gold standard." We decided to use the data for these outcome measures since they were most commonly reported across the included studies; this allowed quantitative comparison between groups in the *meta*-analysis.

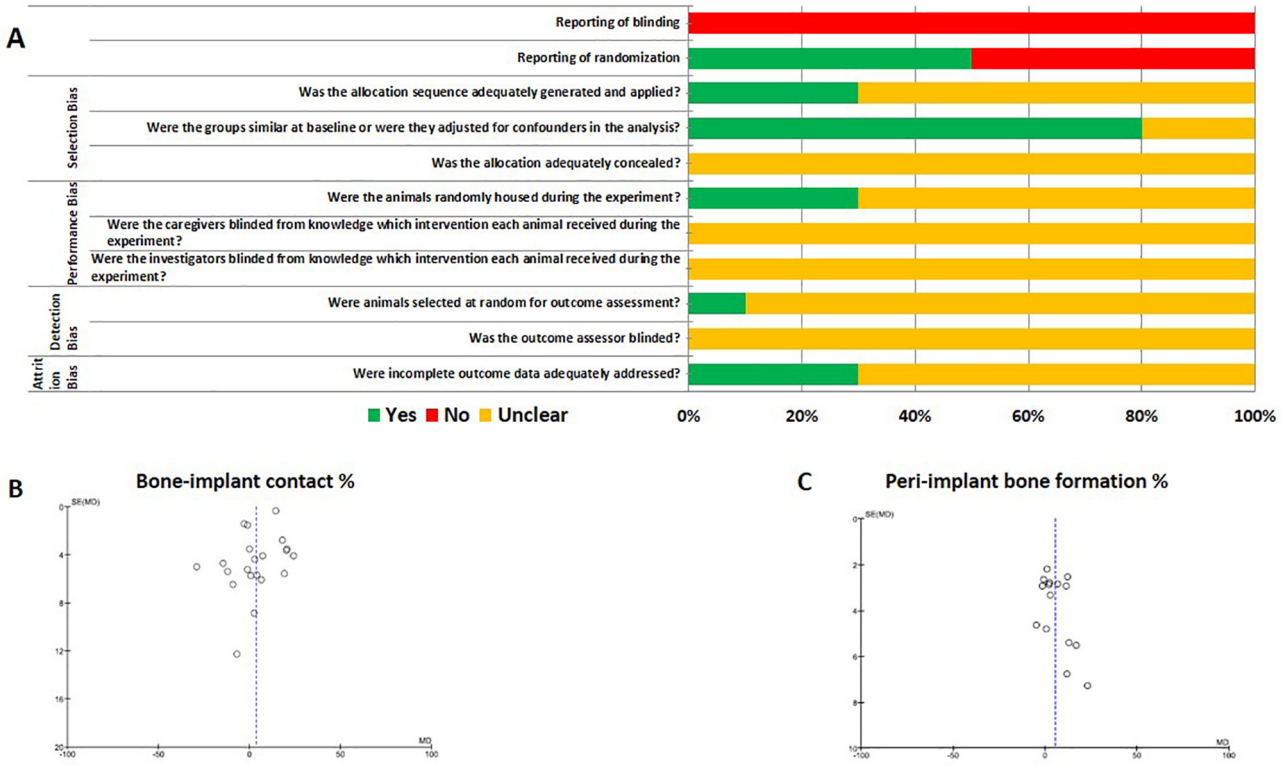

Fig. 2 **A)** Bar-chart shows the assessment of study-quality and risk of bias for the included 10 studies. The first two items are the key study-quality indicators; 'yes' score indicating reported, and 'no' score indicating unreported. The other items assessed risk of bias; 'yes' indicating low risk of bias, 'no' indicating high risk of bias, and 'unclear' risk of bias. **B)** Funnel plots for the BIC data obtained through *meta*-analysis. The vertical line indicates the random effect estimate (I2 > 95%). MD, mean difference; SE, standard error. **C)** Funnel plots for the BF data obtained through *meta*-analysis. The vertical line indicates the random effect estimate (I2 > 71%). MD, mean difference; SE, standard error.

Table 2 Number of comparisons/Implants as measured for each outcome variable. Effect estimate *meta*-analysis presented as mean difference (MD) and 95% confidence interval (CI) according to overall implant comparison and showed positive, negative and no effect.

Group	Number of Comparisons	Number of Implants	Effect Estimate MD [95%CI]	Heterogeneity (I^2)	Positive effect (+ve)	Negative effect (-ve)	No effect
Bone-implant contact (BIC%)	21	348	3.63 [-1.66, 8.91]	95%	6	11	4
Pri-implant bone formation (BF%)	15	264	5.43 [2.20, 8.67]	71%	6	0	9

For histomorphometrical measurements, BIC is defined as the percentage of implant surface in contact with the bone. However for porous-surface implants this measure also includes the pore's perimeter and interior (Vasconcellos et al., 2010). On the other hand, BF is calculated as the bone percentage within a defined *peri*-implant area between the implant threads and/or within the porous implant and extending lateral to the implant for a distance equal to the depth of the threads.

It is well known that a good alternative for a rough coating implant surface is the porous surface since it is can increase the interfacial resistance between the bone and implant material. This results in a more effective and stable implant. Other advantages of a porous surface include a shorter initial healing time, efficient fixation, and increased cellular adhesion potential and vascularization (de Vasconcellos et al., 2010). On the other hand, solid (non-porous surface) implants allow bone to grow onsite only. Since porous implants have been developed so that they can be stabilized by bone growth in the pores, they also result in longer osseointegration (Brentel et al., 2006). For over a decade, this surface modification has been used to stabilize orthopedic implants (Bobyn et al., 1999; Levine et al., 2006), so researchers have developed highly surface-porous implants with trabecular bone-like surface topography (Trabecular Metal Zimmer®, Dental Implant System, Parsippany, NJ, USA), which improves the dental implant's biomechanics and biological properties by increasing surface interactions with the bone tissue (Levine et al., 2006;

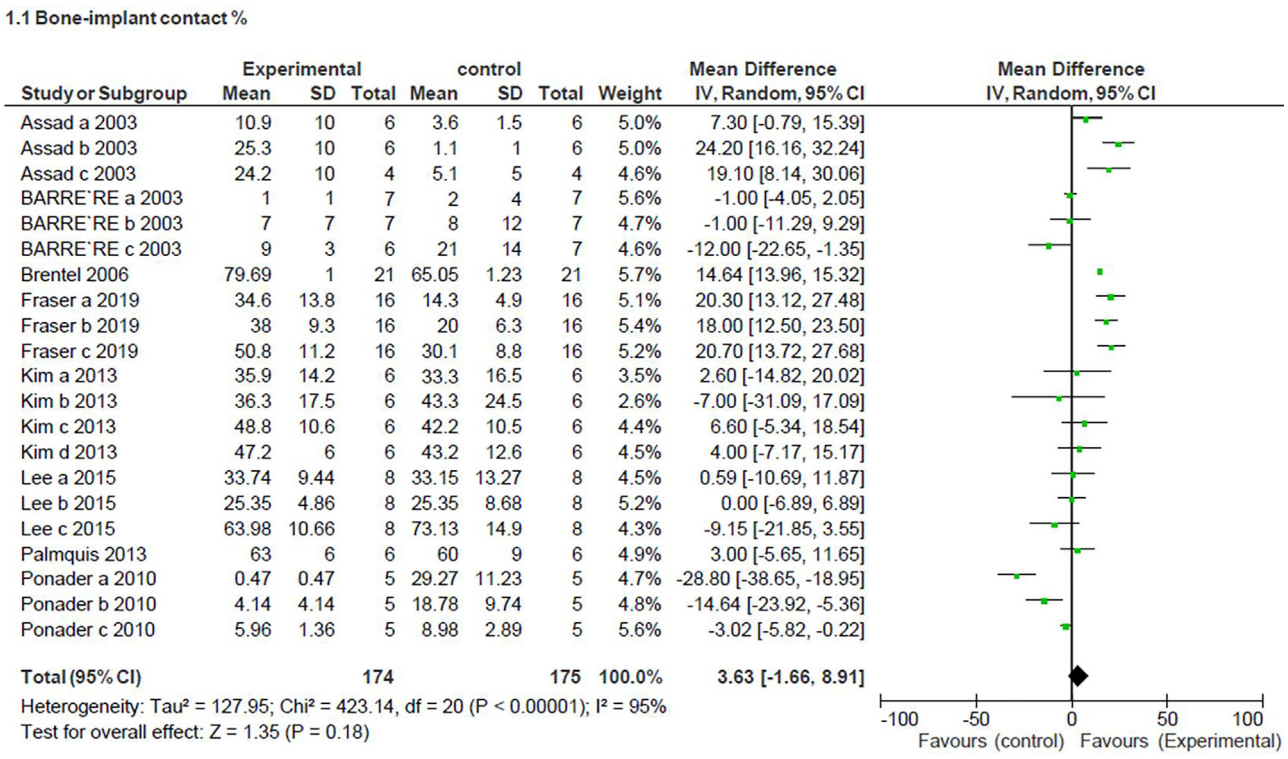

Fig. 3 Forest plots for an overview of the data obtained through *meta*-analysis: histomorphometrical bone-implant contact (BIC); CI, confidence interval; IV, intervention; SD, standard deviation.

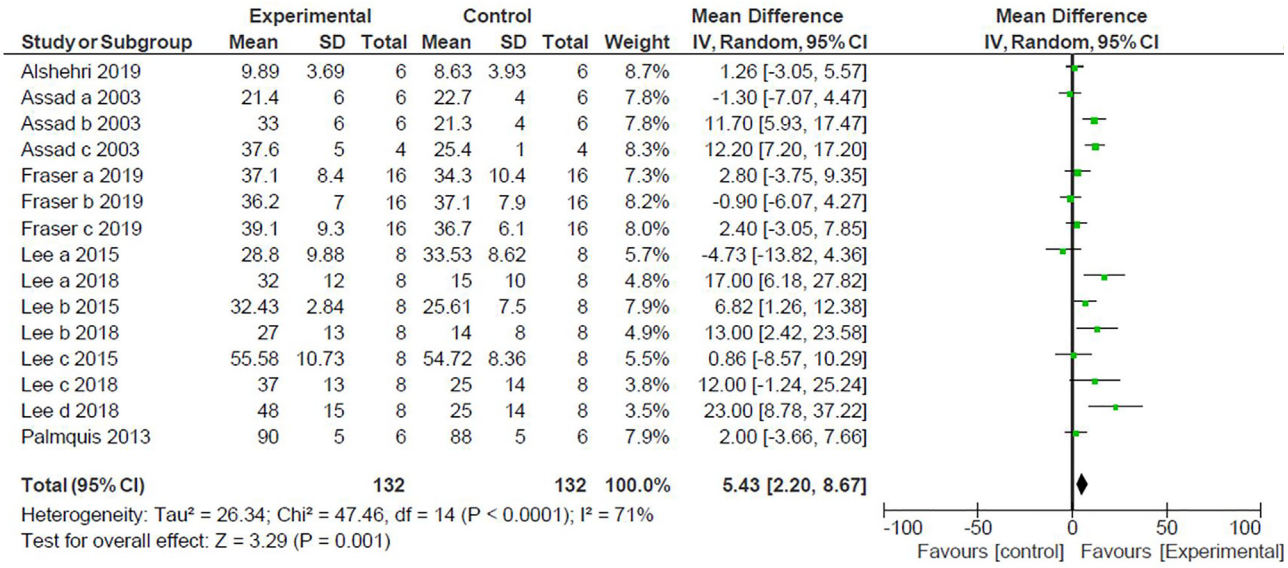

Fig. 4 Forest plots for an overview of the data obtained through *meta*-analysis: histomorphometrical *peri*-implant bone formation (BF); CI, confidence interval; IV, intervention; SD, standard deviation.

Schlee et al., 2015). The concept of integrating porous tantalum trabecular metal (PTTM) into a titanium implant fixture was initially used in orthopedic treatment (Matassi et al., 2013; Bencharit et al., 2014). The trabecular structure of the PTTM dental implants improves osseointegration by increasing bone-implant interface area in a 3D manner, which stimulates angiogenesis and mimics a natural osseous structure. The porous metal structure of the implants is comparable to that of natural spongy bone, due to which osseous ingrowth occurs readily (Bencharit et al., 2014), compared to a non-porous

metal structure. The literature on PTTM as an orthopedic implant material shows that it has great biocompatibility, osteoconductivity, bone ingrowth, and vascularization both *in vitro* and *in vivo* and in human studies (Bobyn et al., 1999; Levine et al., 2006). PTTM results in enhancement of both bone growth and bone ingrowth on the implant surface. Its structure also allows neovascularization and new bone formation directly into the implant, which is known as "osseoincorporation" (Cohen, 2002; Lee et al., 2018).

The present *meta*-analysis has some limitations that should be considered. For example, the results are based on a small number of pooled data (only ten studies using different implantation animal models). The presence of high heterogeneity may be caused by variations in animal models, different anatomical sites of implantation, different healing periods, and different outcome measures.

Additionally, factors such as the reporting quality of the articles and the possibility of publication bias cannot be ignored. Due to the generally poor reporting on blinding and randomization, we were unable to determine the risk of bias for all the included studies. Moreover, we extracted several comparisons from a limited number of studies. Therefore, the results should be interpreted with caution.

5. Conclusion

The results of this *meta*-analysis indicate that BF% improved during implant osseointegration when porous-surface implants are used, compared to implants without a porous surface. For BIC%, no significant difference was found between the two types of implants. Further pre-clinical trials are required to evaluate the benefits of using the porous-surface implant and its promotive effect on osseointegration.

CRediT authorship contribution statement

Abeer Ahmed: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Writing - original draft, Writing - review & editing. **Abdulaziz Al-Rasheed:** Conceptualization, Supervision, Validation, Visualization, Writing - review & editing. **Mohammed Badwelan:** Investigation, Methodology, Software, Validation. **Hamdan S Alghamdi:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Disclosure Statement

No competing financial interests exist.

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