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RESEARCH ARTICLE

A systematic review on the effect of inorganic surface coatings in large animal models and meta-analysis on tricalcium phosphate and hydroxyapatite on periimplant bone formation

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Abstract

The aim of the present systematic review was to analyse studies using inorganic implant coatings and, in a meta-analysis, the effect of specifically tricalcium phosphate (TCP) and hydroxyapatite (HA) implant surface coatings on bone formation according to the PRISMA criteria. Inclusion criteria were the comparison to rough surfaced titanium implants in large animal studies at different time points of healing. Forty studies met the inclusion criteria for the systematic review. Fifteen of these analyzed the bone-to-implant contact (BIC) around the most investigated inorganic titanium implant coatings, namely TCP and HA, and were included in the meta-analysis. The results of the TCP group show after 14 days a BIC being 3.48% points lower compared with the reference surface. This difference in BIC decreases to 0.85% points after 21–28 days. After 42–84 days, the difference in BIC of 13.79% points is in favor of the TCP-coatings. However, the results are not statistically significant, in part due to the fact that the variability between the studies increased over time. The results of the HA group show a significant difference in mean BIC of 6.94% points after 14 days in favor of the reference surface. After 21–28 days and 42–84 days the difference in BIC is slightly in favor of the test group with 1.53% points and 1.57% points, respectively, lacking significance. In large animals, there does not seem to be much effect of TCP-coated or HA-coated implants over uncoated rough titanium implants in the short term.

KEYWORDS
animal experiments, bone-to-implant contact, calcium phosphate coatings, dental implants, implant surface

1 | INTRODUCTION

The success of dental implants depends on a fast and successful osseointegration, meaning the establishment of direct bone-to-implant contact (BIC) without the interposition of connective tissue.[1-3] Osseointegration is known to be influenced by multiple factors, among them implant design,[4,5] surgical technique,[6,7] bone type,[6,8] and loading conditions of the implant.[5,9] In the context of this study the effect of the implant surface[10-13] was the main focus.

Implant surface features that influence osseointegration can be divided into topographical (e.g., roughness), physicochemical (e.g., wettability), and chemical ones (e.g., chemical composition), and all have been varied over a wide range to improve bone implant response[14] and to thus reduce the intervals between implant placement and functional loading.[15,16]

One common method to modify implant surfaces is the use of inorganic coatings consisting of different calcium phosphate phases (CPP) based on the structural, chemical, mechanical and functional similarities to bone mineral and the formation of a biological apatite layer.[17,18] The most investigated coatings of this type are hydroxyapatite (HA, $Ca_5[PO_4]_3OH$) and tricalcium phosphate (TCP, $Ca_3[PO_4]_2$).[15,16,19-21] HA is the most common and well-known phase and is characterized by a Ca/P ratio of 1.67. TCP is characterized by a Ca/P ratio of 1.5 and exists in two allotropic forms depending on temperature: a high-temperature modification, α-TCP (α-$Ca_3[PO_4]_2$), which is fabricated at temperatures in excess of 1,125°C and a low-temperature modification, β-TCP (β-$Ca_3[PO_4]_2$), fabricated at temperatures below 1,125°C.[22] β-TCP is in contrast to α-TCP thermodynamically stable in a biological environment and within a normal temperature range. Another difference is the faster biodegradation of β-TCP compared with α-TCP. A-TCP hydrolyses either partially or completely to hydroxyapatite and the resulting crystals have a non-physiological morphology, which are not resorbed due to their very low level of solubility and may enter the lymphatic system by phagocytosis.[23,24]

HA and TCP ceramics are characterized by the fact that they induce active composite osteogenesis in the biological system, that is, there is generally extensive bone growth without the formation of an insulating intermediate layer. Despite their similar chemical composition, the two calcium phosphates differ in their solubility behavior and in some relevant physical properties, such as density and strength. The resorption rate of calcium phosphate biomaterials is related to their forms and chemical composition as well as to structures including macropores and micropores, with both cell-mediated resorptions and chemical dissolution involved in the resorption process.[25-28] TCP for instance—especially β-TCP ceramic—has a higher resorption rate than HA and can therefore be regarded as a resorbable biomaterial.[25,29-36] The degradation is caused by bone-degrading cells (osteoclasts) as well as by dissolution and subsequent metabolism of the resulting solution products. The minor degradation processes of HA are almost completely attributed to cellular absorption in a much slower process.[37-40] This mainly non-resorptive attribute of HA in body fluid can be unfavorable to the host tissue surrounding the implant, but the more resorbable β-TCP also has its disadvantages, here mainly due to its highly unpredictable resorptive behaviour.[41] The addition of CPP changes not only the chemical composition of the implant surfaces and as a consequence the physicochemical properties such as wetting behavior or surface charge, but also notably the surface roughness. The surface roughness of titanium implants affects the rate of osseointegration and biomechanical fixation, and titanium implants with roughened surface have greater contact with bone than titanium implants with smooth surfaces.[21] Bioceramic coatings have in general been shown to be beneficial for the bone response during the initial healing period after implant insertion,[42] improving cell attachment, extracellular matrix production, BIC and biomechanical fixation in comparison to non-coated implants.[43-48] But as described above, CPP properties can vary strongly depending upon the type, which may well be expected to have consequences with regard to bone response. As an example, CPP-coatings generated by conventional techniques such as plasma spraying may cause clinical problems due to decortication of coating fragments and subsequent inflammatory reactions,[49-51] a problem that does not occur for thinner coatings generated by ion-beam, laser, and sputtering methods.[41,52,53]

In the last two decades much research on inorganic coatings has been done, but its benefits are still a controversial issue. There are many individual studies on this topic with different outcomes, but to the best of our knowledge no statistical meta-analysis. The aim of the present systematic review and meta-analysis is to summarize the current knowledge from large animal studies conducted between 2003 and 2016, analyzing the BIC around HA and TCP titanium implant coatings compared with uncoated rough titanium reference, in order to identify significant differences between coatings at different time points of healing.

2 | MATERIALS AND METHODS

2.1 | Eligibility criteria

The present systematic review was limited to studies that fulfilled the following inclusion criteria: publication period between January 1, 2003, and December 31, 2016; English language; large animal studies with at least six systemically non-compromised animals per study; comparison between inorganic implant surface coatings to an uncoated titanium reference implant. Exclusion criteria was another study designs: studies in humans, rodents, rabbits, in vitro studies, reviews, or studies containing solely organic surface coatings.

This systematic review complies with the criteria of the "Preferred Reporting Items for Systematic Review and Meta-Analysis" (PRISMA).[54]

2.2 | Literature search protocol

An electronic search was conducted in the databases Biosis, Medline (Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE), and Scopus.

TABLE 1 Search pathway

#	Searches	Results
1	Dental Implants/ or exp Dental Implantation, Endosseous/ or exp Denture Design/ or (dental adj3 implant*).ti,ab. Or dental prosthesis design.mp. or (("Protheses and Implants"/ or Prothesis Design/ or Implants, Experimental/ or [implant or implants].tw.) and (dental or dentistry).ab,jn,kw,ti,sb.)	48,077
2	Coated Materials, Biocompatible/ or exp Biomimetics/ or exp Calcium Phosphates/ or exp Hydroxyapatites/ or ((surface* or implant*) adj3 (coated or coating or lining or covering or covered or plating or finishing or loaded or loading or sputter*)).tw. or ([pulse* pr spray* or beam or assisted] adj5 deposit*).tw. or (exp Body Fluids/ or [body adj3 fluid*].tw.) and simulated .tw.) or (surface or coated or coating or lining or covering or covered or plating or finishing or loaded or loading or sptter*).tw. or ((calcium or ca or tricalcium or triple or octacalcium) adj3 (phosphate* or orthophosphate*)).tw.or whitlockite.tw.or (alveograf or calcitite or durapite or hydroxyapatite or hydroxylapatite or "interpore 200" or "interpore 500" or "interpore-200" or "interpore-200" or "interpore-500" or "interpore200" or "interpore500" or osprovit or "ossein hydroxyapatite" or "ossein-hydroxyapatite" or ossopan or ostegen or periograf or algipore or alveoform or "phosphate hydroxide" or "decalcium dihydroxide hexakis" or "hydroxyl apatite" or "hydroxyl apatite" or "osteograf n" or ostim or periograf or radiesse or "tri tab" or "win 40,350").tw. or inorganic.tw.	1,402,858
3	1 and 2	11,560
4	(Animals/ not exp Rodentia/) or (dog* or canine or hound* or hog* or swine* or pig* or porcine or cat* or feline or goat* or caprine or sheep* or ovine).tw.	4,998,289
5	3 and 4	2,582
6	Limit 5 to yr = "2003"	78
7	5	2,582
8	Limit 7 to yr = "2003-Current"	1,695

The detailed search strategy in each case is shown in Table 1.

2.3 | Study selection

Following the automated literature search, titles and abstracts of identified studies were manually and independently screened by three assessors (JD, JN, and GJ) for agreement with the inclusion criteria, with each assessor screening one third of the articles. In case of doubt, full-texts were studied and disagreement was resolved by discussion. Each publication was collected in a software database (EndNote X8; Thomson Reuters). The detailed flow diagram showing the search strategy according to the PRISMA guidelines is given in Figure 1.

2.4 | Data extraction

The following parameters were extracted: animal species, animal number, implant localization, mode of healing, loading (yes/no), follow-up time (days), total implant number, number of different surfaces, type of inorganic surface, type of titanium reference surface, method of qualitative implant analysis, and method of quantitative implant analysis.

2.5 | Meta-analysis

Random effects meta-analyses investigating the difference of change in bone-to-implant contact BIC [% points] between reference (uncoated rough titanium) and test (TCP and HA coated titanium, respectively) implant surfaces were performed.

Three examination time points were defined: T1: 14 days, T2: 21–28 days, and T3: 42–84 days. Paired (one animal received more than one treatment) and unpaired (one animal received one treatment) samples were analyzed in the same meta-analysis. The intra-cluster correlation for the paired studies was not corrected because we could not estimate it from the published data. Accordingly, the 95% CI's can be assumed to be conservative estimates in the cases of paired data. Diagnostic plots (funnel plot, radial plot, standardized residuals, and normal qq plot) were used to check model assumptions and sources of bias. All statistical analysis and figures were performed using the statistical software R,[55] including the package metafor.[56]

3 | RESULTS

As there was a high heterogeneity of the CPP-coatings, not all could be included in the meta-analyses. In order to provide conclusive comparisons, meta-analyses were only performed for the two most common coating types (HA and TCP), while the rest of the coatings were included in the systematic review.

3.1 | Part I—Systematic analysis

3.1.1 | Study selection

The literature search resulted in a total number of 4,174 titles of which 2,815 titles remained after automatic deduplication. Two

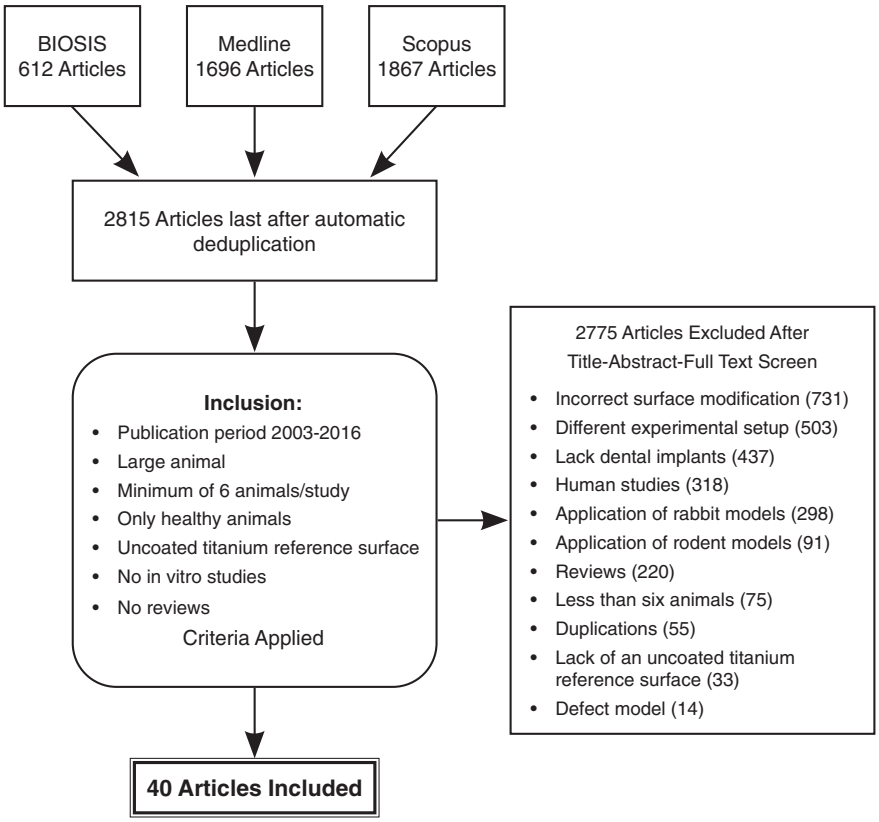

FIGURE 1 PRISMA guidelines

thousand seven hundred and seventy five studies were excluded, the remaining 40 studies[44,57-95] were included in this systematic review. The main cause for exclusion was the application of different surface modifications, for example, the lack of an inorganic test surface (731). Other reasons for exclusion were: different experimental setup, for example, in vitro studies (503), studies without implant like biomaterials (437), human studies (318), rabbit (298) or rodent models (91), reviews (220), studies with less than six animals (75), duplications (55), the lack of an uncoated titanium reference surface (33), or the use of an defect model (14).

3.1.2 | Overview of studies included in the systematic review

Forty studies[44,57-95] were ultimately included in this part (Table 2). Extracted were animal parameters (species, total number, and health condition), implant parameters (material, total number, design, length, diameter, localization, healing mode, and loading), data analysis (examination time and method), and implant surface parameters (number of tested surfaces per study, type of reference surface, type of test surface, and coating components).

Animal parameters

The total number of animals differed between 6 and 24 (mean 10.5) animals. For all studies, animals were systemically healthy with no compromised bone, and no defect models were applied. Four different animal species were used; dog models (30 studies) were the most common, followed by goat (5 studies) and sheep (3 studies) animal models. The smallest groups were pig (1 study) and mini-pig models (1 study).

Implant parameters

The tested number of implants per study varied between nine to 432 implants with a mean of 66.5. Of all tested implants 63 were not osseointegrated and therefore could not be analyzed. All 40 studies[44,57-95] used titanium implants, two studies further applied zirconia implants.[70,76] In 32 studies the implant design was screw-shaped, seven studies used cylinder-shaped implants, only one study used screw-shaped and cylinder-shaped implants.[67] The mean reference implant length in 38 studies was 9.62 mm and the mean test implant length was 9.25 mm. Two studies gave no further information on the implant length.[76,85] The mean implant diameter was 3.79 mm for the reference implant and 3.73 mm for the test implant.

In 20 studies, implants were placed intraorally, in 20 studies extraorally. Most of the intraoral implants were placed in the mandible. Only one study placed implants just in the maxilla,[73] one study placed implants both in the mandible and the maxilla.[57] For studies using extraoral implant sites, implants were placed in the following sites: tibia (7 studies), pelvis (4 studies), femur (4 studies), radius (4 studies), and skull (1 study). In most studies submerged implant healing was chosen. Four studies chose non-submerged healing.[58,59,67,91] In two studies half of the implants were loaded with

TABLE 2 List of the 40 studies included in the systematic review

No.	Author	Year	Title
1	Abrahamsson et al.[57]	2013	Deposition of nanometer scaled calcium-phosphate crystals to implants with a dual acid-etched surface does not improve early tissue integration
2	Al-Hamdan et al.[58]	2011	Effect of implant surface properties on peri-implant bone healing: a histological and histomorphometric study in dogs
3	Al-Hamdan et al.[59]	2012	Effect of implant surface properties on peri-implant bone healing: implant stability and microcomputed tomographic analysis
4	Alghamdi et al.[60]	2013	Biological response to titanium implants coated with nanocrystals calcium phosphate or type 1 collagen in a dog model
5	Artzi et al.[61]	2011	Clinical and histomorphometric observations around dual acid-etched and calcium phosphate nanometer deposited-surface implants
6	Barros et al.[62]	2009	Effect of biofunctionalized implant surface on osseointegration: a histomorphometric study in dogs
7	Bonfante et al.[63]	2013	Buccal and lingual bone level alterations after immediate implantation of four implant surfaces: a study in dogs
8	Coelho et al.[64]	2009	Early healing of nanothickness bioceramic coatings on dental implants. An experimental study in dogs
9	Coelho et al.[65]	2011	Bone mineral apposition rates at early implantation times around differently prepared titanium surfaces: a study in beagle dogs
10	Coelho et al.[66]	2010	Biomechanical and bone histomorphologic evaluation of four surfaces on plateau root form implants: an experimental study in dogs
11	Coelho et al.[67]	2011	The effect of different implant macrogeometries and surface treatment in early biomechanical fixation: an experimental study in dogs
12	Coelho et al.[68]	2012	Biomechanical and histologic evaluation of non-washed resorbable blasting media and alumina-blasted/acid-etched surfaces
13	Danna et al.[69]	2015	Assessment of atmospheric pressure plasma treatment for implant osseointegration
14	Ferguson et al.[70]	2008	Biomechanical comparison of different surface modifications for dental implants
15	Foley et al.[71]	2010	Effect of phosphate treatment of acid-etched implants on mineral apposition rates near implants in a dog model
16	Granato et al.[72]	2009	Biomechanical and histomorphometric evaluation of a thin ion beam bioceramic deposition on plateau root form implants: an experimental study in dogs
17	Im et al.[73]	2015	A comparative study of stability after the installation of 2 different surface types of implants in the maxillae of dogs
18	Junker et al.[74]	2011	Bone reaction adjacent to microplasma-sprayed calcium phosphate-coated oral implants subjected to an occlusal load, an experimental study in the dog
19	Junker et al.[75]	2010	Bone-supportive behavior of microplasma-sprayed CaP-coated implants: mechanical and histological outcome in the goat
20	Langhoff et al.[76]	2008	Comparison of chemically and pharmaceutically modified titanium and zirconia implant surfaces in dentistry: a study in sheep
21	Marin et al.[77]	2013	Histologic and biomechanical evaluation of 2 resorbable-blasting media implant surfaces at early implantation times
22	Marin et al.[78]	2010	Biomechanical and histomorphometric analysis of etched and non-etched resorbable blasting media processed implant surfaces: an experimental study in dogs
23	Nergiz et al.[79]	2009	Stability of loaded and unloaded implants with different surfaces
24	Nikolidakis et al.[80]	2008	Effect of platelet-rich plasma on the early bone formation around Ca-P-coated and non-coated oral implants in cortical bone
25	Ozeki et al.[81]	2006	Bone response to titanium implants coated with thin sputtered HA film subject to hydrothermal treatment and implanted in the canine mandible

(Continues)

TABLE 2 (Continued)

No.	Author	Year	Title
26	Ramazanoglu et al.[82]	2011	The effect of combined delivery of recombinant human bone morphogenetic protein-2 and recombinant human vascular endothelial growth factor 165 from biomimetic calcium-phosphate-coated implants on osseointegration
27	Schliephake et al.[83]	2009	Effect of modifications of dual acid-etched implant surfaces on periimplant bone formation. Part II: calcium phosphate coatings
28	Schliephake et al.[84]	2003	Biological performance of biomimetic calcium phosphate coating of titanium implants in the dog mandible
29	Schliephake et al.[85]	2006	Biomimetic calcium phosphate composite coating of dental implants
30	Schmitt et al.[86]	2016	In vivo evaluation of biofunctionalized implant surfaces with a synthetic peptide (P-15) and its impact on osseointegration. A preclinical animal study
31	Schouten et al.[87]	2009	Effects of implant geometry, surface properties, and TGF-β1 on peri-implant bone response: an experimental study in goats
32	Sieber et al.[44]	2007	In vivo evaluation of the trabecular bone behavior to porous electrostatic spray deposition-derived calcium phosphate coatings
33	Song et al.[88]	2016	Osseointegration of magnesium-incorporated sand-blasted acid-etched implant in the dog mandible: resonance frequency measurements and histomorphomtetric analysis
34	Van Oirschot et al.[89]	2016	Comparison of different surface modifications for titanium implants installed into the goat iliac crest
35	Von Salis-Soglio et al.[90]	2014	A novel multi-phosphonate surface treatment of titanium dental implants: a study in sheep
36	Wang et al.[91]	2015	Effects of fluoride-ion-implanted titanium surface on the cytocompatibility in vitro and osseointegatation in vivo for dental implant applications
37	Witek et al.[92]	2013	Surface characterization, biomechanical, and histologic evaluation of alumina and bioactive resorbable blasting textured surfaces in titanium implant healing chambers: an experimental study in dogs
38	Xiropaidis et al.[93]	2005	Bone-implant contact at calcium phosphate-coated and porous titanium oxide (TiUnite)-modified oral implants
39	Zechner et al.[94]	2003	Osseous healing characteristics of three different implant types: a histologic and histomorphometric study in mini-pigs
40	Zhang et al.[95]	2013	The synergistic effect of hierarchical micro/nano-topography and bioactive ions for enhanced osseointegration

prefabricated crowns after healings periods of six[74] and 13[79] weeks. Two studies placed implants immediately after tooth extraction.[91,97]

Healing time points

The studies used one, two, three or four healing time points for analysis (T1, T2, T3, and T4). The earliest time point of examination was after two days, the latest time point of implant examination was after 490 days. Mean T1 implant healing time point was 17.2 days. In 28 studies a second time point was analyzed (mean T2: 63.42 days). A third examination time point was analyzed in 10 studies (mean T3: 113.2 days). Only one study had a fourth examination point (T4: 168 days).[81] Most studies used qualitative histology and quantitative histomorphometry, analyzing the BIC and in some cases the bone volume. Other methods of analysis were radiographic, fluorochrome labeling, and mechanical testing such as removal torque test. The histological examination was performed by 36 studies, histomorphometry by 31 studies. Eight studies performed fluorochrome labeling, 17 studies performed mechanical testing, 10 studies used radiography, and no study used immunohistochemistry.

Implant surface parameters

Ten non-identical inorganic surface coatings could be identified. Different forms of application were possible for the same inorganic surface coating. Some studies analyzed inorganic surface components as well organic components or in combination. The most investigated inorganic surface coatings were tricalcium phosphate and hydroxyapatite. The authors assigned the surface components to the following four groups: (a) tricalcium phosphate coatings (TCP), (b) hydroxyapatite coatings (HA), (c) other inorganic coatings (I), and (d) additional organic coatings (O). Table 3 shows the details for the test and reference surfaces of all 40 studies. The results of the individual studies per surface group can be found in the Appendix S1.

TABLE 3 Allocation of surface coatings

Study	R	TCP	HA	I	O
1. Abrahamsson et al.[57]	X (***)	X (*)			
2. Al-Hamdan et al.[58]	X (*/**)		X (*****)		
3. Al-Hamdan et al.[59]	X (*/**)		X (****)		
4. Alghamdi et al.[60]	X (***)	X (**)			X (*/**)
5. Artzi et al.[61]	X (***)	X (*)			
6. Barros et al.[62]	X (*/**)		X		X (**)
7. Bonfante et al.[63]	X (*/**; ******)	X (*)	X		
8. Coelho et al.[64]	X (****)	X (*)			
9. Coelho et al.[65]	X (****)	X (*****)	X (*)		
10. Coelho et al.[66]	X (****; *****)	X (*; ***)			
11. Coelho et al.[67]	X (****)	X (********)		X (*)	
12. Coelho et al.[68]	X (****)	X (*********)			
13. Danna et al.[69]	X (*/**)	X (*; *******)	X (*; *******)		
14. Ferguson et al.[70]	X (*/**)	X (**)		X (*******; ********)	X (*/**; */******)
15. Foley et al.[71]	X (***)			X (***)	
16. Granato et al.[72]	X (****)	X (*****)			
17. Im et al.[73]	X (*/**)	X (********)			
18. Junker et al.[74]	X (***)	X (***/****)			
19. Junker et al.[75]	X (***)	X (***; ****)			
20. Langhoff et al.[76]	X (*/**)	X (**)		X (*******; ********)	X (*/**; */******)
21. Marin et al.[77]	X (****)	X (********)			
22. Marin et al.[78]	X (****)	X (********)			
23. Nergiz et al.[79]	X (*; *****)		X (*; ******)		
24. Nikolidakis et al.[80]	X (****)	X (******)			X (****)
25. Ozeki et al.[81]	X (****)		X (*****)		
26. Ramazanoglu et al.[82]	X (***)	X (*)			X (***)
27. Schliephake et al.[83]	X (***; *****)		X (***)		X (*/**) (*/*****)
28. Schliephake et al.[84]	X (*****)		X (***)		X (*/**; */*****)
29. Schliephake et al.[85]	X (*****)		X (***)		X (*/**; */*****)
30. Schmitt et al.[86]	X (*/**; *****)		X (***)		X (**)
31. Schouten et al.[87]	X (*****)	X (**)			X (***)
32. Sieber et al.[44]	X (*******)	X (**)			
33. Song et al.[88]	X (*/**)	X (********)		X (**)	
34. Van Oirschot et al.[89]	X (*/**)		X (*****)	X (*)	
35. Von Salis-Soglio et al.[90]	X (*/**; *****)			X (***)	
36. Wang et al.[91]	X (*****)			X (****)	
37. Witek et al.[92]	X (****)	X (********)			
38. Xiropaidis et al.[93]	X (******)	X (******)			
39. Zechner et al.[94]	X (*****; ******)		X		
40. Zhang et al.[95]	X		X (*)	X (*****; ******)	

Note: Titanium reference surface (R): *microrough**-grit-blasted/acid-etched (SLA); ***dual acid-etched; ****alumina-blasted/acid-etched; *****polished-machined; ******pure titanium/anodic oxidation; ******* plasma-sprayed. Tricalcium phosphate (TCP): *discrete deposition; **electrostatic spray deposition; ***plasma-sprayed****-micro-plasma-sprayed; *****ion-beam assisted deposition; ******RF magnetron sputter deposition; *******atmospheric pressure plasma treated; ********resorbable-blasting media; *********non-washed resorbable-blasting media. Hydroxyapatite (HA): *plasma-sprayed**-micro-plasma-sprayed; ***electrochemical assisted deposition; ****ion-beam assisted deposition; *****RF magnetron sputter deposition; ******sol–gel deposition; ******* atmospheric pressure plasma treated. Other inorganic surfaces (I): *bioactive ceramic electrodeposition; **magnesium; ***phosphonate; ****fluoride; *****hardystonite; ******strontium; *******bisphosphonate, ********plasma anodized. Organic surfaces (O): *extracellular matrix**-collagen type 1; ***-collagen type 2; ****-collagen type 3, *****-HA mineralized collagen, ******-chondroitin sulfate; ** peptide surface coating; *** growth factor surface coating; **** platelet-rich plasma.

TABLE 4 List of the 15 studies included in the meta-analysis

Study	Surface-coating	Animal model	Location	Examination time points (days)	More than one examination time point per animal
Abrahamsson et al.[57]	TCP	Dog	Mandibula	14, 28	Yes
Al-Hamdan et al.[58]	HA	Dog	Mandibula	14, 28, 56	No
Barros et al.[62]	HA	Dog	Mandibula	56	No
Bonfante et al.[63]	TCP + HA	Dog	Mandibula	14, 28	Yes
Coelho et al.[64]	TCP	Dog	Tibia	14, 28	Yes
Danna et al.[69]	TCP	Dog	Radius	21, 42	Yes
Granato et al.[72]	TCP	Dog	Tibia	14, 28	No
Junker et al.[75]	TCP	Goat	Femur	42	No
Langhoff et al.[76]	TCP	Sheep	Pelvis	14, 28, 56	No
Nikolidakis et al.[80]	TCP	Goat	Tibia	42	No
Ramazanoglu et al.[82]	TCP	Pig	Calvaria	14, 28	No
Schliephake et al.[83]	HA	Dog	Mandibula	28, 84	No
Siebers et al.[44]	TCP	Goat	Femur	84	No
Van Oirschot et al.[89]	HA	Goat	Iliac crest	28	No
Xiropaidis et al.[93]	TCP	Dog	Mandibula	56	No

3.2 | Part II—Meta-analysis results

Table 4 shows the details to all 15 studies[44,57,58,62-64,69,72,75,76,80,82,83,89,93] included in the meta-analysis.

3.2.1 | TCP 14 days

The overall BIC of the test surface was 3.48% points lower compared with the reference surface (95% CI: −7.62, 0.67). However, the overall difference in BIC% points between test and control implants after 2 weeks of healing was statistically not significant ($p = .1$) (Figure 2).

The highest BIC in favor of the test surface is shown by Ramazanoglu et al.[82] showing a wide confidence interval that overlaps the no effect line.

3.2.2 | TCP 21 to 28 days

The overall BIC of the test surface was 0.85% points lower compared with the reference surface (95% CI: −6.46, 4.77). However, the overall difference in BIC% points between test and control implants at three to four weeks of healing was statistically not significant ($p = .76$) (Figure 3).

Danna et al.[69] revealed a statistically significant larger effect for the coated test group with 12% points (95% CI: 3.08, 20.92) whereas Abrahamson et al.[57] showed an opposite effect with −9.40% points for the coated test group (95% CI: −15.53, −3.27). Danna et al.[69] is the only study in this group to investigate the time point 21 days, whereas the other studies investigated the time point 28 days. Abrahamson et al.[57] and Bonfante et al.[63] were the only two studies in this group using the mandible as implant site and showed the highest values in favor of the reference surface.

3.2.3 | TCP 42 to 84 days

The overall BIC of the coated test surface was 13.79% points higher compared with the reference surface (95% CI: −1.83, 29.41). However, the overall difference in BIC% points between test and control implants at 6–12 weeks of healing was statistically not significant ($p = .08$) (Figure 4).

Junker et al.[75] and Danna et al.[69] found a statistically significant larger effect for the coated test group with 38.10% points (95% CI: 21.23, 54.97) and 25.00% points (95% CI: 16.08, 33.92) respectively. Xiropaidis et al.[93] measured an opposite effect with −14.10% points (95% CI −26.85, −1.35) for the coated test group. The studies examining the earliest possible healing time in this group (42 days) show the greatest effect in favor of the test surface. Xiropaidis et al.[93] showed the highest BIC in favor of the reference surface, which was the only study in this group that used the mandible as implant site.

3.2.4 | Hydroxyapatite 14 days

The overall BIC of the coated test surface was 6.94% points lower compared with the reference surface (95% CI: −11.18, −2.70). The overall difference in BIC% points between test and control implants at 2 weeks of healing was statistically significant ($p = .001$) (Figure 5).

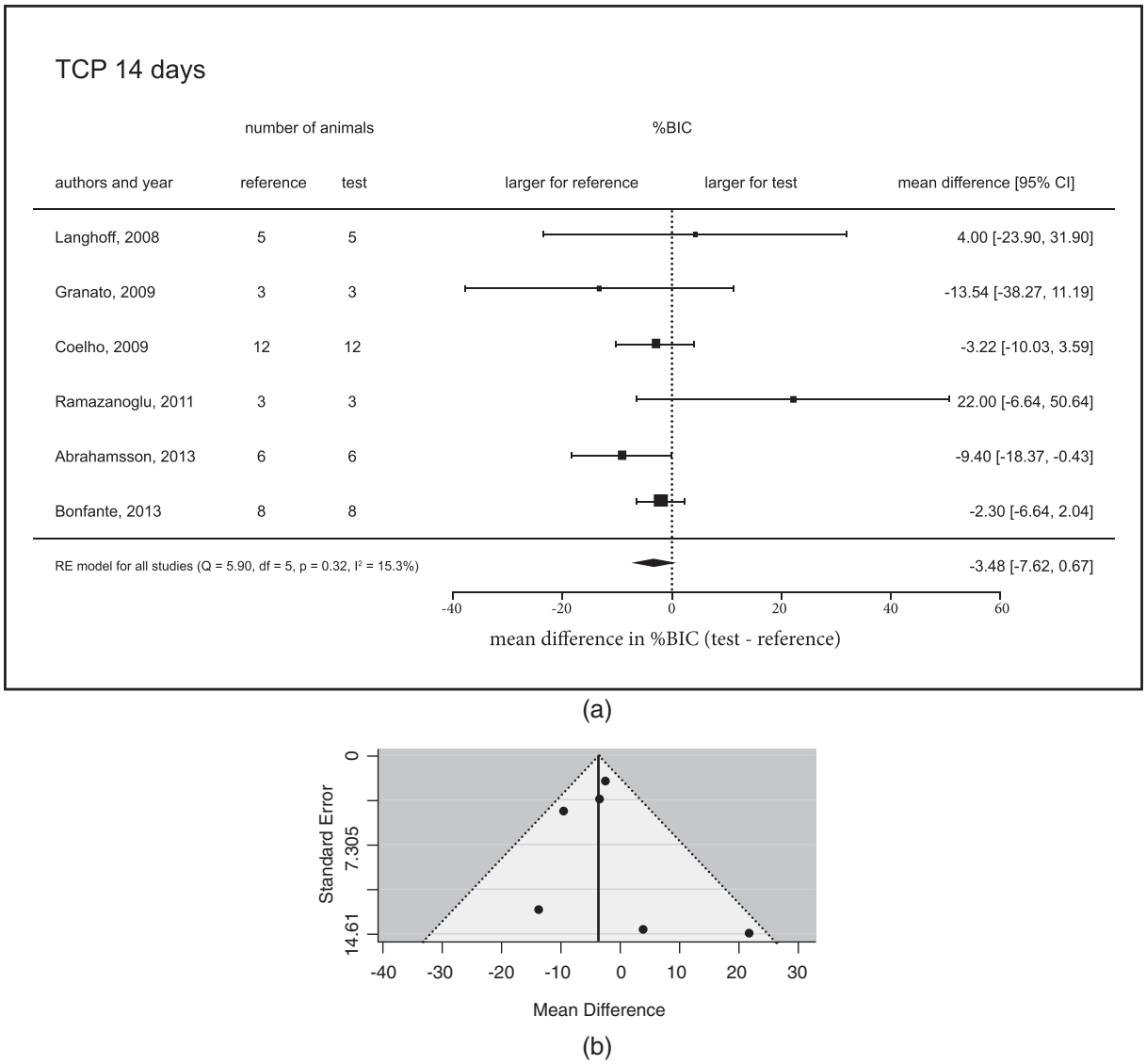

FIGURE 2 (a) Overall results of the meta-analysis of TCP after 14 days of all test surfaces compared with all reference surfaces. (b) Funnel plot of the results of TCP after 14 days illustrates the standard error versus the mean difference of the studies

Bonfante et al.[63] showed a statistically significant larger effect for the uncoated reference group with −7.00% points (95 CI: −11.34, −2.66).

3.2.5 | Hydroxyapatite 21 to 28 days

The overall BIC of the coated test surface was 1.53% points higher compared with the uncoated reference surface (95% CI: −4.28, 7.34). However, the overall difference in BIC% points between coated test and uncoated control implants at 4 weeks of healing was statistically not significant ($p = .61$) (Figure 6).

3.2.6 | Hydroxyapatite 42 to 84 days

The overall BIC of the coated test surface was 1.57% points higher compared with the uncoated reference surface (95% CI: −5.02, 8.17). However, the overall difference in BIC% points between test and control implants at 6–12 weeks of healing were statistically not significant ($p = .64$) (Figure 7).

3.3 | Publication bias

In most of cases the funnel plot did not indicate any publication bias, though especially for the HA meta-analyses this must be viewed with caution due to the limited number of studies. The only exceptions were the groups TCP 21–28 days and TCP 42–84 days. The funnel plots of these two groups illustrate some large heterogeneity. At times, the small studies demonstrate a lower variation in their estimation of the treatment effect compared with the larger studies. This could be due to heterogeneity in the study designs (although much caution was taken to select and categorize similar studies) but is also difficult to conclusively assess due to the limited number of studies (Figures 2b–7b; Appendix S1).

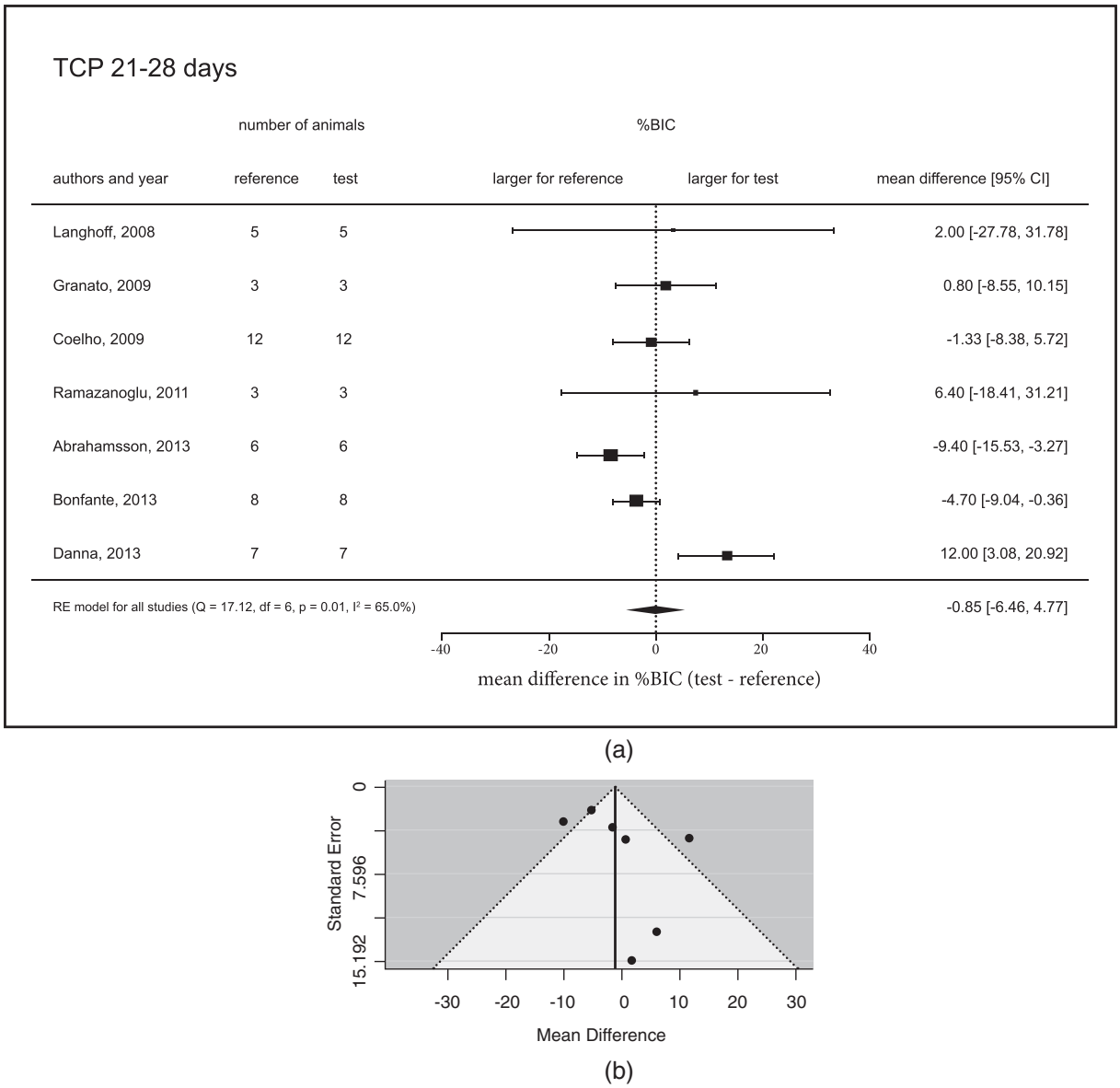

FIGURE 3 (a) Overall results of the meta-analysis of TCP 21–28 days of all test surfaces compared with all reference surfaces. (b) Funnel plot of the results of TCP 21–28 days illustrates the standard error versus the mean difference of the studies

4 | DISCUSSION

4.1 | Effect of coating

Many studies evaluate the effect of implant surface modifications on the bone–implant interaction. The development of implant surface coatings is an effort to induce an optimal interaction between bone and the implant surface. Various research groups focus on the development of inorganic surface coatings, as these surface coatings may improve bone formation.

The present meta-analysis evaluated whether the two most commonly applied inorganic surface coatings, TCP and HA, improve periimplant bone formation in large animals at three different time points of healing in comparison to uncoated titanium surfaces. Interestingly the results of this meta-analysis show, that the overall BIC did not show a relevant increase for TCP-surfaces or HA-surfaces at the different time points, although individual studies included in this study had significant effects of TCP-surface or HA-surface coatings. However, the TCP group shows an increasing advantage of the test surface over the uncoated reference over time, whereas the differences in the HA group remain comparably small. The positive biological effects from HA-coating to improve osseointegration, such as the capacity of adsorbing proteins, the improvement of osteoblast proliferation, the enhancement of bone formation and the reduction of bone loss could be well characterized,[21,34,98-101] but were not reflected by the periimplant bone formation represented by the BIC value.

After an observation period of 14 days the TCP-coatings showed a 3.48% points lower mean BIC compared with the reference group.

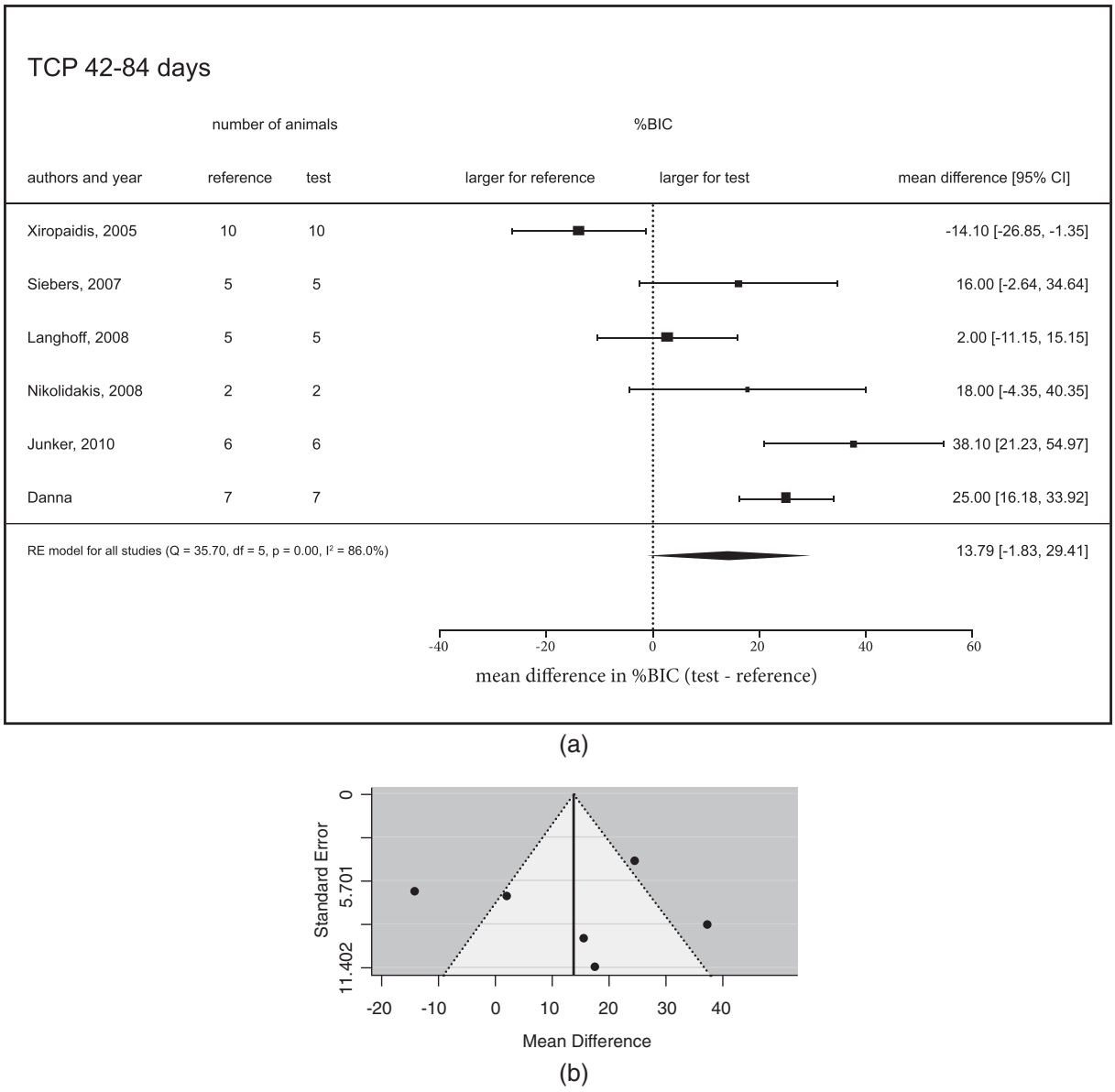

FIGURE 4 (a) Overall results of the meta-analysis of TCP 42 or more days of all test surfaces compared with all reference surfaces. (b) Funnel plot of the results of TCP 42 or more days illustrates the standard error versus the mean difference of the studies

After 21–28 days, TCP-coatings still showed a 0.85% points lower mean BIC compared with the reference group. Only after 42–84 days there was positive change in favor of the TCP group, showing a difference of 13.79% points to the reference group. However, the results were not significant and the variability between the studies increased over time. The meta-analysis of HA-coatings showed a similar pattern, although the differences in % points at the different time points of investigation were not as broad. After 14 days the difference in % points of BIC was 6.94 in favor of the reference surface. In the observation period of 21–28 days, there was a slight difference in favor of the test group of 1.53% points. This was with 1.57% points also the case after 42–84 days. Only the difference after 14 days was statistically significant, but with only two included studies, this result should be viewed with caution. It should be mentioned that there were more study results for the TCP group compared with the HA group, which could affect these estimates.

One possible explanation for the fact that no relevant effects on periimplant bone formation were found in this study could be that only studies using a rough titanium surfaced reference implants were included in the meta-analysis. This is in difference to many other studies that analyzed the effect of CPP-coatings, as they compared biomimetically coated implants to uncoated reference implants with a smooth surface. The studies Schliephake et al.[84,85] investigated HA-coatings using smooth surfaced reference implants (polished and machined, respectively). As these studies did not use a rough reference surface, they were excluded from this meta-analysis. Both studies showed significantly higher values for the coated implants after 4 weeks compared with the smooth reference surface. After

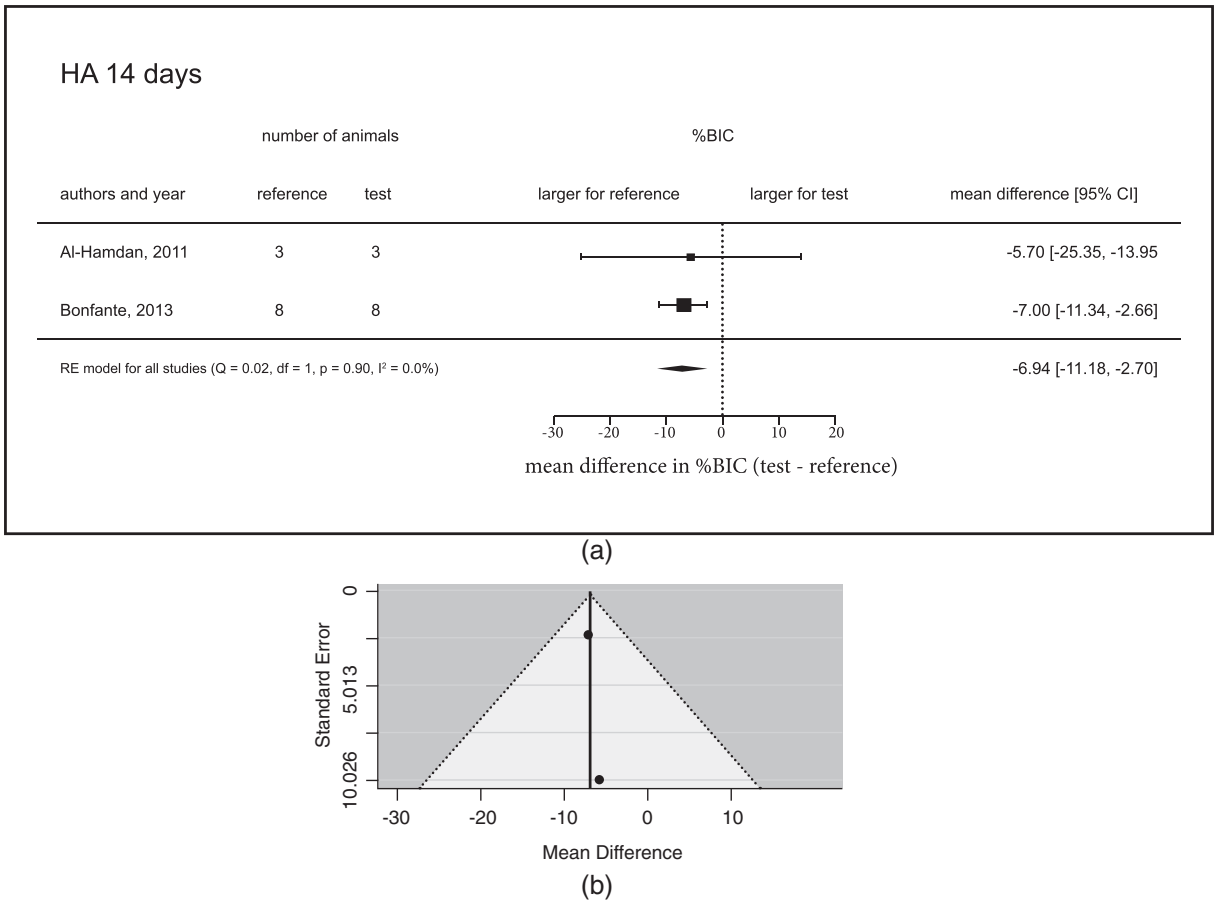

FIGURE 5 (a) Overall results of the meta-analysis of HA after 14 days of all test surfaces compared with all reference surfaces. (b) Funnel plot of the results of HA after 14 days illustrates the standard error versus the mean difference of the studies

12 weeks, only the study of 2006[85] still showed significant differences. The authors concluded that composite coating implant surfaces with HA could enhance BIC, most notably in the early ingrowth period. In the present meta-analysis using rough reference surfaces we made a different observation: a difference in BIC in favor of the test surface was only present at later time points.

Zechner et al.[94] also used machined surfaced (MS) implants and anodized titanium surface implants as controls against HA-coated implants. The histomorphometric evaluation of the BIC showed significant differences between machined surface and HA-coated implants as well as between machined surface and anodically modified surfaces. The authors concluded that an anodically roughened implant surface might provide a comparable rate of BIC compared with HA-coated implants. The study could not be included in the present meta-analysis although it fulfilled the inclusion criteria due to unattributed implant losses, which could not be assigned to the different examination time periods. Schliephake et al.[83] analyzed MS implants and implants with a dual acid-etched (DAE) surface, being compared with HA-coatings. After 1 month of healing, the BIC of implants with a DAE surfaces and additional hydroxyapatite coating was significantly higher compared with MS implants but did not differ significantly from implants with sole DAE. After 3 months only the comparison of HA-coated implants to MS implants showed a significant increase in BIC. This was not the case when compared with implants with a DAE coating. The study indicates that an increase in bone formation of experimental coatings and the DAE control surface over MS was limited to early stages of periimplant bone formation. The data of the rough reference surfaces (DAE) and HA-coatings was included in the meta-analysis. It is shared by various studies that an increase in surface roughness increases the bone formation and mechanical interlocking[102,103] and that rougher surfaces achieve higher bone mechanical properties at earlier time points compared with smooth surfaces.[104] Smooth surfaces consequently show a lower BIC formation[83,97]: the bone-to-implant contact of titanium implant surfaces such as sandblasted and acid etched surfaces (large grit; HCL/H_2SO_4) (50–60%) and HA-coated implants (60–70%) is significantly superior to sandblasted with a large grit and titanium plasma-sprayed implants (30–40%) or electro polished and sandblasted and acid etched (medium grit; HF/HNO_3) implants (20–25%). It was assumed that the BIC value is positively correlated with an increasing roughness of the implant surface.[105] This is correct up to a certain degree of roughness. Over the years, moderately rough surfaces have shown the best clinical characteristics with regard to periimplant bone.[106,107] This well-documented effect of surface roughness may explain why inorganic coatings did not lead to increased periimplant bone formation in this study, as the

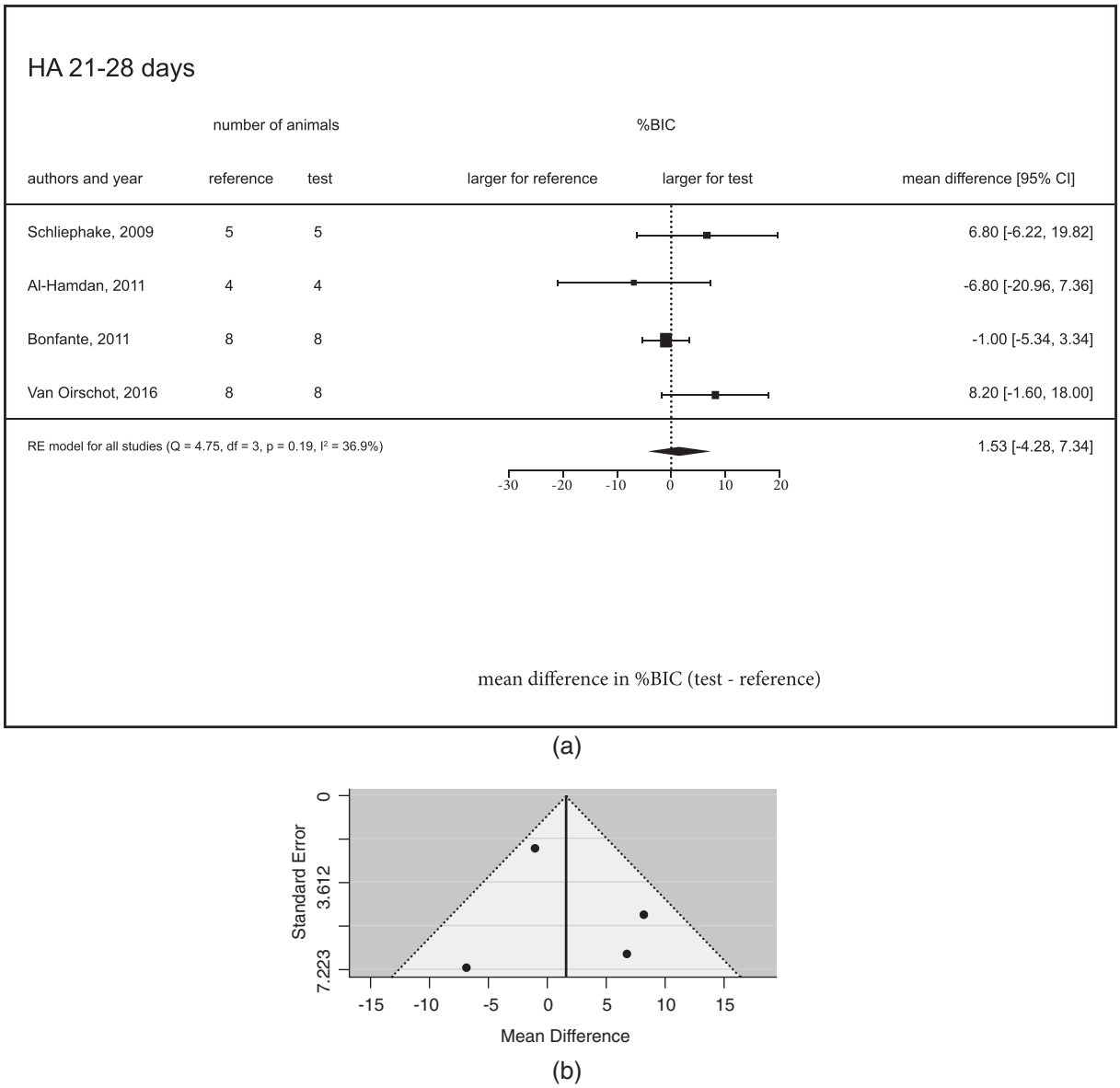

FIGURE 6 (a) Overall results of the meta-analysis of HA 21–28 days of all test surfaces compared with all reference surfaces. (b) Funnel plot of the results of HA 21–28 days illustrates the standard error versus the mean difference of the studies

effect of roughness may overshadow the potential positive effect of the CPP-coatings.[31,34]

It should also be considered that the studies used partially different approaches for preparing CPP-coatings and depending on the surface coating technique, different coatings are generated. Theses surfaces show differences regarding their chemical composition, surface roughness, coating thickness, and morphology. The ability of osteoconductivity of HA-coatings depends on various factors, such as crystallinity, solubility, and stability,[10] and on the thickness and electrical polarization of the HA surface,[108] which all differ with the method of deposition. In addition, various techniques require different post-deposition treatments such as heat. High temperatures can have an impact on the integrity of the bonding between the bioactive surface layer and the implant surface. This could cause resorption, re-absorption, and degradation of the coating in a biological environment and may affect the longevity of an implant.[109] Although this meta-analysis showed an increasing difference between test and reference surface over time, the longevity of CPP-coating remains controversial.[110] An optimal technique for the application of bioactive surface coatings has not been developed. Therefore, also the deposition technique of different coatings needs to be considered when comparing the bone formation around inorganic coatings.

TCP- or HA-coatings can be regarded as scaffold for bone-forming cells that can enhance early osseointegration of an implant[111] but seem to have no clinical advantage over rough implants. However CPP-based biomaterial seems to be efficient drug delivery vehicles as, for example, for growth factors.[112] The natural tissue repair process requires numerous signaling molecules and growth factors, in a time and concentration-dependent form.[113-115] Therefore the future of bioactive implants may be a combination of inorganic and organic

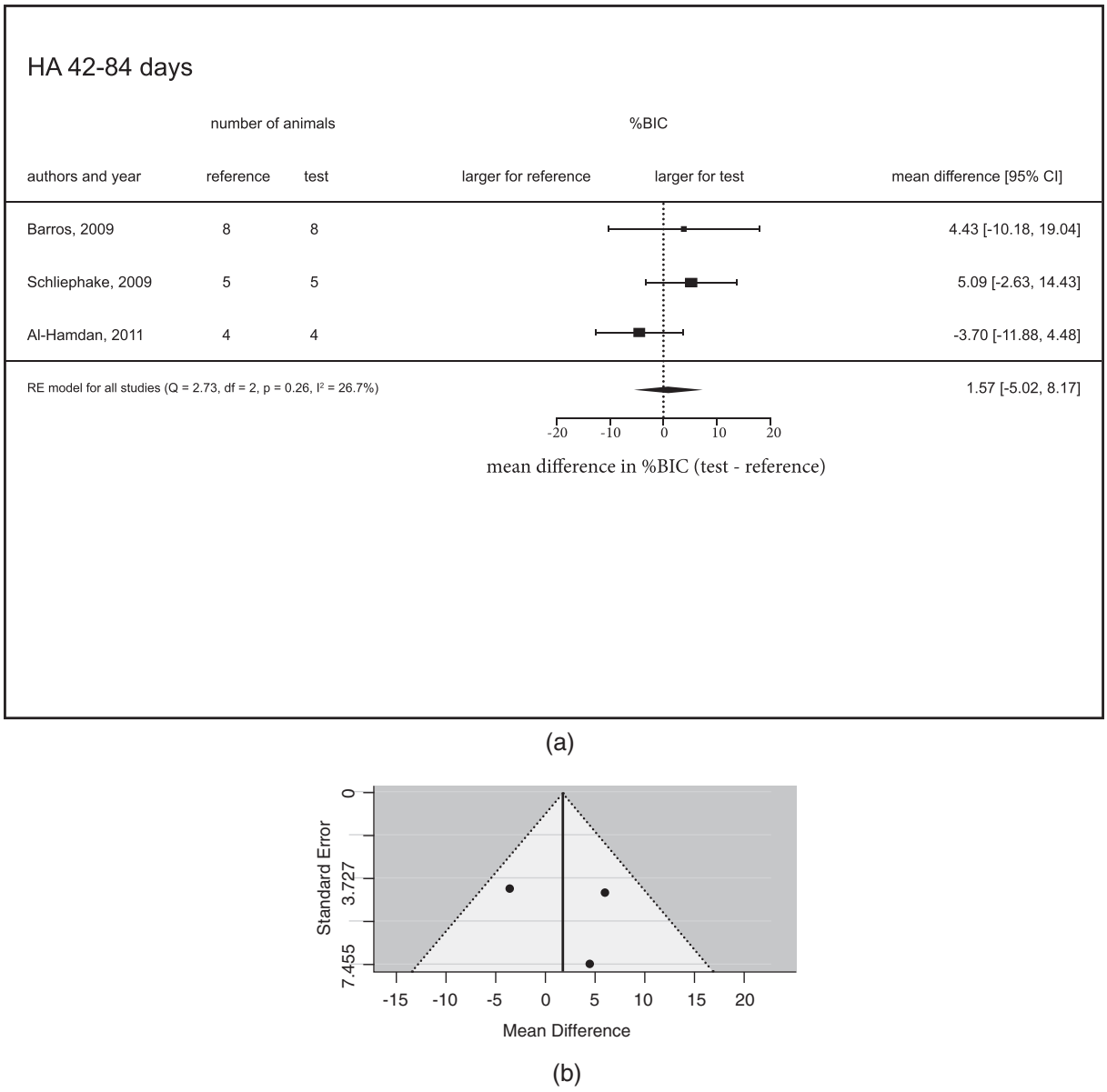

FIGURE 7 (a) Overall results of the meta-analysis of HA 42 or more days of all test surfaces compared with all reference surfaces. (b) Funnel plot of the results of HA 42 or more days illustrates the standard error versus the mean difference of the studies

components to result in truly bone-resembling coatings, leading to improved biological activity and functionality.[111]

4.2 | Effect of animal model

Prior to clinical use in humans, animal models are often applied for testing dental implants. Finding the ideal animal model can be difficult due to the necessary similarities to humans, both in terms of physiological and pathological considerations, as well as being able to observe numerous subjects over a relatively short period of time.[116-118] Different large animal models were integrated in this meta-analysis, observing the possible differences in BIC. The most frequently applied animal model in the meta-analysis was the dog model. The second most frequently applied animal model was the goat model, followed by sheep and pig models. All animals were systemically unimpaired.

Studies on TCP-coatings included in the meta-analysis used dog, sheep, goat, and pig models (Table 4). Over all time periods, with one exception (Danna et al.)[69], the dog model appeared to favor the reference surface, while sheep, goat, and pig studies all showed a small effect in favor of the coated test surface. These differences may be due to the differences in the rate of bone turnover and the remodeling activity between the species. Aerssens et al.[119] found that canine bone most closely resembles human bone when comparing the bone composition of numerous species, but also porcine bone demonstrates similarities in bone mineral concentration and in bone mineral density to human bone. Comparing the bone regeneration rate of dogs, pigs, and humans, Laiblin et al.[120] found that pigs have a more

similar rate of bone regeneration with humans compared with dogs (dog: 1.5–2.0 mm/day; pig: 1.2–1.5 mm/day; human: 1.0–1.5 mm/day). Therefore, the noticed BIC may not solely represent the actual effect of a specific type of surface coating on osseointegration.

Studies on HA-coatings included in this meta-analysis all used dog models, with the exception of van Oirschot et al.[89] who used a goat model (Table 4). The study of van Oirschot et al.[89] only occurs in the 21–28 day group, but shows the highest BIC values in favor of the test surface, however the difference is not significant. As van Oirschot et al.[89] already discussed, the bone formation in the used crestal bone of goats has superior site-specific osteogenic properties and thus possibly overshadows the benefits of the HA-coating used.[96] Similar to the TCP-group, the studies that used dog models show better BIC values for the reference surface, especially at the first time of examination. The difference between reference and test surface at this time point was significant. Over time, the BIC values increased in favor of the test surface, however the differences are not significant.

Differences of the observed effects could also be due to the age of the animals. Age does affect normal bone turnover as well as the bone response in relation to implants material.[121] Therefore it could be essential to have a consistent age of the animals within a study. Differences in bone metabolism due to age may, however, not have an influence on long term implant survival. Clinical studies in patients do not see a significant influence of age on later implant loss.[122,123] This aspect may influence comparisons between different studies. Studies investigating implants in small animals including rodents and rabbits were excluded from the current review and meta-analysis as bone structure and properties are less similar to humans compared with large animal models.[121]

4.3 | Effect of location

Various anatomical locations may serve for the analysis of osseointegration. The structure of, for example, the jawbone of pigs or dogs is different to humans and the bone quality and dynamics of bone formation may change depending on the anatomical location. In the present meta-analysis, both extra-oral and intra-oral localizations were included.

In the meta-analysis of TCP-coatings, the most commonly used implant sites were the mandible and the tibia (three studies each), followed by the femur (two studies) and the calvaria (one study) (Table 4). Studies, which inserted implants into the mandible, showed better BIC values for the uncoated reference surface at all examination times. In the meta-analysis of HA-coatings most studies used the mandible as implant site, with the exception of van Oirschot et al.[89], using the iliac crest (Table 4). Similar to the meta-analysis of TCP-coatings, studies, which place implants intraorally, tend to show better BIC values for the reference surface. The meta-analysis of HA-coatings contains only two studies at the time of the first examination, both of the studies implanted intraorally. The difference in BIC between the reference and test surface was significant. Over time, the BIC value changed slightly in favor of the test surface, however, the differences were not significant.

A possible explanation for the tendency of lower BIC values of the test surface for intraorally placed implants could be that the biologically active surface coatings tend to promote bacterial adhesion. Cell and bacteria adhesion processes are in fact dependent on the surface condition. Especially the chemical composition, the hygroscopic properties, as well as the roughness of the surface play an important role.[124] Increasing clinical interest, therefore, lies in implant coatings with the properties of improves osseointegration and additional antimicrobial characteristics. Wolf-Brandstetter et al.[125] integrated trace elements of copper and zinc into calcium phosphate based coatings. The authors found a stimulation of angiogenesis, the attraction and stimulation of bone-forming cells, and inhibitory effects on bacteria in close proximity to the implant. However, there have to be further in vivo investigations.

4.4 | Effect of examination time point

For the meta-analysis, three time points of investigation were defined: T1: 14 days, T2: 21–28 days, and T3: 42–84 days as these correspond to the current study designs and enabled the highest possible amount of data. Periods ranging from one day to 6 weeks after implant installation are considered as early healing periods with dynamic processes during tissue integration.[126] The properties of the implants surface are determining for differentiation and adhesion of osteoblasts during the initial phase of osseointegration as well as in long-term bone remodelling.[127,128] It is assumed that inorganic implant surface coatings result in enhanced host-to-implant response at early implantation times. However, the meta-analysis of TCP-coatings did not confirm this expectation and there was no significant increase in BIC values at any time point compared with the rough reference surface. Overall, the BIC values rather increased over time in favor of the test surface, however lacking statistical significance. Danna et al.[69] was the only study showing a significant advantage for the test surface after 21 days. All other studies using the time period of 21–28 days showed no positive effect for the reference surface. Of all time points examined, the highest mean BIC value in favor of the test surface was seen after 42 days, lacking significance.

The meta-analysis for HA-coatings showed a significant increase in BIC for the reference implants after 14 days. Similar to the meta-analysis of TCP-coatings the BIC values increased slightly over time in favor of the test surface but there was no statistically significant difference.

The results do not imply an advantageous effect of CPP-coatings over moderately rough titanium implants on early bone-implant healing.

4.5 | Limitations

The results of this study should be treated with caution, since due to the strict inclusion criteria only few studies could be included. With regard to implant design, especially surface roughness may overshadow the potential positive effect of the biological performance of the inorganic coatings. Additionally, the comparative shortness of the included study times (2 weeks to 3 months) could contribute to the non-

significant outcome. Also the anatomical location of the implant may influence osseointegration as the dynamics of bone formation differ in different locations. There is also little homogeneity in terms of animal species and the type of bone, limiting the interpretation of the results. Furthermore, one should be aware that differences in BIC as a function of healing time or implant surface will not necessarily translate into better biomechanical performance.[17] The variations in BIC values in different animal models could be due to differences in bone regeneration. A further limitation of the interpretation of absolute BIC values is the fact that BIC also is dependent on sample preparation, staining, number of sections per implant and thickness of histological sections.[129] It should also be considered that animal experiments not necessarily reflect the human clinical outcomes. All these factors make the general interpretation of implant surface coating studies difficult and complicates the interpretation of the results.

5 | CONCLUSION

The current systematic review analyzed studies using inorganic implant coatings. The consecutive meta-analysis focused on the effect of TCP and HA implant surface coatings on periimplant bone formation. Aim was to find out whether there is a relevant difference in periimplant bone formation at different time periods. Even though individual studies could report a positive effect of TCP and HA coatings compared with an uncoated reference, it was thus not possible to determining significant relevance based on coating type. The results of the meta-analysis show an increase in differences in BIC for TCP over time, but hardly any for HA. There does not seem to be much advantage of TCP-coated or HA-coated implants over uncoated rough titanium implants in the short term.

The effect of the coating also needs to be explored with regard to possible long-term effects of inorganic implant surfaces. For future approaches, the combination of inorganic coating with proteins, growth factors, and therapeutic agents could be of interest for osseointegration and a reduction of infection.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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