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Meta-Analysis
Dental Implants

Does incorporating collagen and chondroitin sulfate matrix in implant surfaces enhance osseointegration? A systematic review and meta-analysis

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Abstract. Implant surface modification has been used to improve osseointegration. However, evidence regarding improved new bone formation (NBF) and osseointegration with the use of collagen–chondroitin sulfate (CS) matrix coated implants remains unclear. The aim of this study was to assess the efficacy of collagen–CS matrix coating on the osseointegration of implants. The focused question was ''Does the incorporation of collagen–CS matrix in implant surfaces influence osseointegration?'' To answer the question, indexed databases were searched up to July 2017 using various combinations of the key words ''collagen'', ''chondroitin sulfate'', ''osseointegration'', and ''implants''. The initial literature search identified 497 articles, of which 18 reporting experimental studies fulfilled the inclusion criteria. Thirteen of the studies included (72%) reported that implants coated with a collagen–CS matrix presented higher NBF, bone-to-implant contact, and/or bone volume density. The strength of this observation was supported by meta-analysis results. Nevertheless, the results should be interpreted with caution due to the lack of standardization regarding the dosage formulation of collagen–CS, short-term follow-up, and lack of assessment of confounders. On experimental grounds, the incorporation of collagen–CS matrix into implant surfaces appears to promote osseointegration. From a clinical perspective, the results from animal models support phase I studies in healthy humans.

Key words: chondroitin sulfates; collagen; extracellular matrix; implants; osseointegration.

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Dental implants are a well-established and predictable treatment option for the replacement of missing teeth in edentulous patients[1,2]. However, local factors such as residual bone density and/or quantity, new bone formation (NBF), primary stability, and the establishment of direct bone-to-implant contact (BIC) may influence the success and survival of implants[3]. Additionally, systemic disorders such as poorly controlled diabetes mellitus and osteoporosis may also result in challenging bone healing conditions[4–6].

Different biological, physical, and chemical techniques of implant surface modification have been developed with the aim of stimulating osteogenesis and enhancing peri-implant bone formation in systemically healthy, as well as immunosuppressed patients[7–11]. One such technique is the application of coatings with biological components to implant surfaces to enhance the proliferation and differentiation of osteoprogenitor cells, vascularization, and expression of osteogenic genes (which helps to enhance BIC and promote osseointegration)[12,13]. These biological coatings may be either in an inorganic form (hydroxyapatite) or organic form (protein components of the extracellular matrix (ECM) of bone)[14,15].

Type I collagen constitutes approximately 90% of the ECM and is an important structural component of the bone cellular network[16]. Type I collagen induces osteoid formation and mineralization by stimulation of osteoblast proliferation, differentiation, and adhesion, via binding to integrin receptors $\alpha 1\beta 1$ and $\alpha 2\beta 1$[17–19]. Furthermore, type I collagen has been shown to enhance mRNA expression of cellular proteins such as runt-related transcription factor 2, osteopontin, and osteoprotegerin, which may influence bone healing[20].

It has been suggested that incorporating the glycosaminoglycan chondroitin sulfate (CS) into a collagen matrix may promote interactions with tissue growth factors[21]. The highly negative charge of CS sugar chains binds to the positively charged amino acid sequences of mediators (such as fibroblast growth factor, bone morphogenetic proteins, and transforming growth factors), stimulating the ossification process[22,23]. Therefore, the incorporation of collagen–CS matrix into bone cements and implant surfaces has been proposed to enhance their mechanical properties and promote osteogenic cell adhesion, proliferation, and differentiation[24–41]. Moreover, collagen–CS matrix has also been associated with a reduced inflammatory response, due to the interaction of CS with interleukins (mediators associated with inflammation)[42].

In an experimental study on male rats, Rammelt et al. investigated the effect of collagen–CS matrix incorporated into titanium surfaces on implant osseointegration[25]. The results showed higher BIC for collagen–CS coated implants than for control implants (uncoated titanium) and implants coated only with collagen. Likewise, Stadlinger et al. reported higher BIC and bone volume density (bone volume/tissue volume, BV/TV) for titanium implants modified with collagen–CS matrix than for control implants placed in miniature pigs[33]. Similar results have been reported in other preclinical studies[24,26,30,31]. However, conflicting results have also been reported regarding the role of collagen–CS coatings in enhancing osseointegration and NBF around implants. Langhoff et al. reported no significant difference in BIC among uncoated titanium, uncoated zirconia, and collagen–CS coated implants in a sheep model[28].

The aim of this systematic review and meta-analysis was to assess the efficacy of collagen–CS matrix coating on the osseointegration of implants.

Materials and methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[43]. The focused question addressed was: ''Does the incorporation of collagen and chondroitin sulfate matrix in implant surfaces influence osseointegration?''

Eligibility criteria

The inclusion criteria were as follows: (1) original clinical and experimental (animal model) studies; (2) presence of a control group (osseointegration around implants without collagen–CS matrix); (3) intervention: effect of collagen–CS matrix on osseointegration; (4) evaluation of parameters that influence osseointegration (BIC, NBF, and/or BV/TV) in subjects with and without implants coated with collagen–CS matrix. Qualitative and/or quantitative reviews, laboratory-based investigations (in vitro studies), case reports/case series, commentaries, letters to the editor, and interviews and updates were excluded.

Literature search protocol and data extraction

The international prospective register of systematic reviews in health and social care (PROSPERO) and the Cochrane Register of Systematic Reviews were searched in March 2017. No existing reviews assessing the efficacy of collagen–CS matrix coatings on implant osseointegration were registered at that time. In order to identify studies relevant to the focused question, a systematic and structured literature search without language restriction was conducted by two authors (FJ and SVK) using the PubMed (National Library of Medicine, Bethesda), Scopus, Embase, Google Scholar, and Web of Knowledge databases. The databases were searched up to and including July 2017 using different combinations of the following medical subject heading (MeSH) terms: (1) dental implants, (2) chondroitin sulfate, (3) collagen, (4) osseointegration, (5) extracellular matrix, and (6) glycosaminoglycan. Other related non-MeSH terms were used in the search strategy to detect articles discussing bone formation around implants coated with collagen and chondroitin sulfate. These included: (7) implants, (8) new bone formation, and (9) bone to implant contact. Boolean operators (OR, AND) were used to combine the key words mentioned above: (a) 1; 4 OR 7; AND 2 OR 5 OR 6; (b) 1; 4 OR 7 AND 2 AND 3; (c) 1 OR 7 AND 8 OR 9; AND 2; 5 OR 6.

To minimize the potential for reviewer bias, the titles and abstracts of studies identified using the protocol described above were screened independently by two authors (FJ and SVK) and checked for agreement. Full-text articles of those judged by title and abstract to be relevant were read and evaluated independently for the stated eligibility criteria. After the initial electronic search, the reference lists of the studies identified were hand-searched to identify further potentially relevant studies. Any disagreements in the study selection process were resolved by discussion and consensus between the authors (FJ and SVK). Cohen's kappa was used to determine the inter-reviewer reliability ($\kappa = 0.82$)[44]. Data were extracted using standardized evaluation forms. The authors of the studies included were contacted via e-mail in the case of missing data or the requirement for additional information regarding their studies. Fig. 1 summarizes the literature search.

Quality assessment

The Cochrane Collaboration's tool for assessing risk of bias was used to perform a qualitative assessment of the studies included[45]. A structured analysis was conducted using the following criteria: random sequence generation, allocation

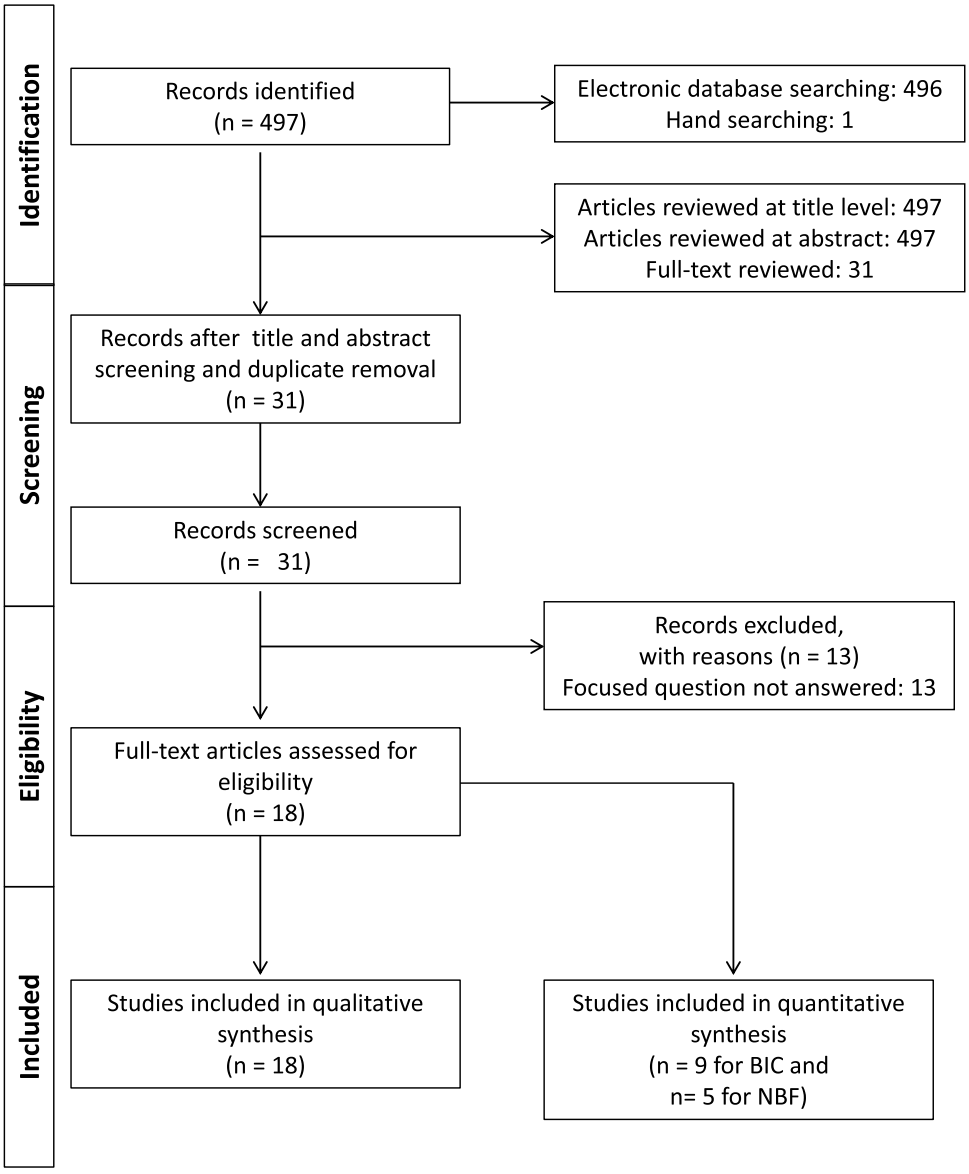


Fig. 1. Flowchart of the article selection process for the systematic review, according to the PRISMA guidelines.

concealment, blinding of study personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. These were classified as adequate (+), inadequate (−), or unclear (?). Based on these criteria, an overall estimation of the risk of bias (low, moderate, or high) was made for each selected study. When all the criteria were met, the risk of bias was considered low. Those studies that partly met one or more criteria and met the remaining criteria were considered to have a moderate risk of bias. The risk of bias was considered high when one or more criteria were not met[45].

Data analysis

Meta-analyses to answer the focused question were conducted for BIC (nine studies[25,29,31–35,37,39]) and NBF (five studies[25,26,32,36,39]). The heterogeneity in the treatment difference between the control and treatment groups across the studies was assessed using the Q statistic. The random-effects meta-analysis model was used to combine the results from the different studies[46]. The analysis was conducted using OpenMetaAnalyst version 6 (open-source software; Brown University, Providence, RI, USA).

Results

Study selection

Through the initial search, 497 potential articles were identified. After title and abstract screening, 466 publications that did not answer the focused question or were duplicates were excluded. In the second step, 13 more articles that did not answer the focused question were excluded. In total, 18 prospective in vivo studies were included and processed for data extraction[24–41].

General characteristics of the studies included

Dogs were the study subjects in three studies, with female dogs in two[24,32] and male dogs in one[39]. Five studies involved sheep; three studies were performed in female sheep[26,28,41] and two studies did not specify the sex[27,38]. Miniature pigs were the subjects in six studies: three were conducted with male and female minipigs[31,33,34], one was performed with female minipigs[37], and the sex was unclear

in two studies[29,30]. Female rats were used as study subjects in two studies[35,36], and male rats in two studies[25,40].

The role of collagen–CS matrix in the promotion of NBF around implants was assessed in healthy animals in 16 studies[24–34,37–41]. The remaining two studies assessed osseointegration in animals with induced osteoporosis[35,36]. The follow-up period in the studies included ranged between 2 days and 24 weeks (Table 1).

Titanium implants with collagen and chondroitin sulfate coated surfaces

Implant and coating-related characteristics

Thirteen studies investigated titanium implants and reported the number used (range 36–224)[25–31,33–35,37–39]. Three studies investigated titanium implants but did not report the number used[24,32,36]. Ten studies reported the implant dimensions (diameter × length in millimeters), which ranged between 1.7 × 3 mm and 5 × 15 mm[27,29–31,33–35,37–39]. Five studies reported only the implant diameter, which ranged between 0.8 mm and 5.5 mm[24–26,32,36]. One study did not report the dimensions of the implants used[28].

The implants were placed in the mandible in eight studies[24,29–33,37,39], the tibia in four studies[25,26,35,36], and the pelvis in two studies[27,28]. In the study by Stadlinger et al., implants were placed in the maxilla of miniature pigs[34]. Liu et al. implanted pedicle screws into the L2–L5 pedicles of sheep[38].

Cylindrical implants were placed in eight studies[27–31,33,34,39], and screw-type implants in five studies[24,32,35,37,38]. Rammelt et al. used screw-type implants to stabilize a midshaft tibial fracture and inserted cylindrical implants into the tibial head[26]. Two studies implanted 0.8-mm diameter pins[25,36]. Rough-surfaced implants were used in 12 studies[26–31,33–35,37–39], and smooth-surfaced implants were used in three[24,25,36]. One study used smooth- and rough-surfaced implants[32]. In seven studies, implants were modified to create longitudinal grooves, longitudinal recesses, or circular chambers, in order to allow the analysis of bone formation in the peri-implant space and/or the assessment of osteoinductive and osteoconductive properties of the surface modifications (Table 2)[24,29–34].

The collagen coatings on the Ti substrate were prepared by fibrillogenesis with bovine skin type I collagen, at a concentration ranging between 1 mg/ml and 5 mg/ml, in nine studies[25,26,29–31,33–36]. Two studies used type I collagen from rat tail, with concentrations of 2 mg/ml and 1 mg/ml, respectively[37,38]. Schliephake et al. anchored porcine type I collagen on the Ti implant surface by adsorption and anodic polarization[32]. In the study by de Barros et al., type II collagen from chicken sternal cartilage was dissolved at 1 mg/ml in 10 mM acetic acid[39]. The type of collagen and/or the method used to incorporate collagen into Ti surfaces remained unclear in three studies[24,27,28].

Eleven studies incorporated CS from bovine trachea during the fibrillogenesis process[25–27,29–31,33–36,38]. Two studies used CS from porcine trachea[37,39]. Three studies did not report the origin of CS incorporated into the Ti surfaces[24,28,32].

Assessment of osseointegration

Osseointegration was assessed using histomorphometric analysis in 13 studies[24,25,29–39], and using histological analysis in 10 studies[24–26,28,32–34,36,37,39]. In four studies, biomechanical testing (pull-out or removal torque) was performed to assess NBF and the strength of newly formed bone around implants[26,27,35,38]. Four studies assessed NBF around implants by synchrotron radiation micro-computed tomography[26,29,30,36], and one study assessed this using scanning nanoindentation[36]. Fluorochrome labeling was used in two studies to assess NBF and the mineralization process around the implants[28,39]. Three studies used micro-computed tomography to assess NBF[27,35,38]. Implant stability was measured by resonance frequency analysis in two studies[29,33].

Main outcomes

The results of 11 studies showed that collagen–CS coated titanium implants enhanced NBF, BV/TV, and/or BIC around implants[24,25,29–34,36,37,39]. Five studies reported no detectable impact on osseointegration for implants coated with collagen–CS, with similar outcomes in terms of NBF, BV/TV, and/or BIC compared to uncoated implants[26–28,35,38]. Three studies reported that collagen–CS enhanced the strength of fixation on implants[26,35,38]. Ferguson et al. reported lower extraction torque in implants coated with collagen–CS compared with uncoated Ti implants[27].

Hydroxyapatite implants with collagen and chondroitin sulfate

Implant-related characteristics

Two studies prepared a fiber-reinforced composite with calcium-deficient carbonated hydroxyapatite (originated from the setting of calcium phosphate bone cement in simulated body fluid), freeze-dried mineralized type I collagen (2.5 wt%), and 5 mg of chondroitin-4-sulfate per gram cement[40,41]. In one study, 60 cylinders (2 × 6 mm) were placed in rat tibiae[40]. In the other study, 14 cylinders (2.5 × 30 mm) with an 8-mm central hole were placed in sheep tibiae[41].

Assessment of osseointegration

Osseointegration was assessed using histological and histomorphometric analyses in both studies[40,41]. Schneiders et al. also used computed tomography, immunohistochemistry, and enzyme histochemistry to assess NBF around modified hydroxyapatite implants[41].

Main outcomes

Both studies involving hydroxyapatite implants modified with collagen–CS reported higher BIC and NBF compared with hydroxyapatite implants modified with collagen alone[40,41]. In one study, the number of osteopontin-positive osteoblasts was significantly higher around hydroxyapatite implants modified with collagen–CS[41].

Meta-analyses

Meta-analyses were performed of the nine studies reporting mean and standard deviation BIC values[25,29,31–35,37,39], and the five studies reporting NBF around titanium implants with and without collagen–CS coatings[25,26,32,36,39].

With regard to BIC, the sample sizes were comparable in all of the studies. The reported mean BIC value in the test group was higher than that in the control group in eight of the nine studies. The Q statistic showed that the treatment effects differed significantly among the nine studies ($Q = 19.4$, $P = 0.01$). The random-effects model showed that the combined BIC in the test group was extremely significantly higher than that in the control group (mean difference = −6.6, $P < 0.01$) (Fig. 2).

With regard to NBF, the reported mean NBF value was higher in the test group than in the control group in all five studies. The Q statistic showed that the treatment effects did not differ significantly among

Table 1. General characteristics of the studies included in the review.

Authors (year)	Study subjects (Mean age)	Study groups	Collagen and chondroitin sulfate form (concentration)	Follow-up (weeks)	Analysis methods	Outcome
Titanium implants with collagen and chondroitin sulfate coated surfaces surfaces						
Schliephake et al.[24] (2005)	10 female dogs (NA)	Group 1: uncoated Ti Group 2: Ti + CI Group 3: Ti + CI + CS + BMP-2	NA	Up to 12	Histology HIST	Groups 2 and 3 presented higher BIC and BV/TV compared with group 1
Rammelt et al.[25] (2006)	72 male rats (NA)	Group 1: uncoated Ti Group 2: Ti + CI Group 3: Ti + CI + CS Group 4: Ti + RGD peptide	CS from bovine trachea (10% mass) CI from bovine skin (1 mg/ml)	Up to 4	Histology HIST	Group 3 presented higher BIC compared with groups 1, 2 and 4 BV among all the groups was comparable
Rammelt et al.[26] (2007)	6 female sheep (NA)	Group 1: uncoated Ti Group 2: Ti + CI Group 3: Ti + CI + CS Group 4: Ti + HA	CS from bovine trachea (10% mass) CI from bovine skin (1 mg/ml)	Up to 6	Removal torque Histology SRμCT	Groups 3 and 4 presented higher extraction torque compared with groups 1 and 2 NBF among all the groups was comparable
Ferguson et al.[27] (2008)	15 sheep (NA)	Group 1: uncoated Ti Group 2: uncoated Zr Group 3: Ti + CaP Group 4: Ti + CaP + APC Group 5: Ti + alendronate Group 6: Ti + CI + CS	CS from bovine trachea (30 μg/mg) CI: NA (2.5 mg/ml)	Up to 8	Removal torque Micro-CT	Group 6 presented higher removal torque compared with groups 2 and 4, but lower than groups 1, 3 and 5 BV/TV among all the groups was comparable
Langhoff et al.[28] (2008)	15 female sheep (24 to 36 months old)	Group 1: uncoated Ti Group 2: Ti + CaP Group 3: Ti + CaP + APC Group 4: Ti + collagen + CS Group 5: Ti + alendronate Group 6: uncoated Zr	NA	Up to 8	Fluorochrome labeling Radiographs Histology	No significant difference in BIC among all the groups
Stadlinger et al.[29] (2007)	20 minipigs (12 months old)	Group 1: Ti + CI Group 2: Ti + CI + CS Group 3: Ti + CI + CS + BMP-4	CS from bovine trachea (30 μg/mg) CI from bovine skin (5 mg/ml)	Up to 22	HIST SRμCT RFA	Group 2 presented higher BIC compared with groups 1 and 3 BV/TV was higher in group 1 compared with groups 2 and 3 Comparable ISQ among all groups
Stadlinger et al.[30] (2008a)	8 minipigs (12 months old)	Group 1: Ti + CI Group 2: Ti + CI + decorin Group 3: Ti + CI + CS Group 4: Ti + CI + decorin + TGF-β1 Group 5: Ti + CI + CS + BMP-4 Group 6: Ti + CI + CS + decorin + TGF-β1 + BMP-4	CS from bovine trachea (30 μg/mg) CI from bovine skin (5 mg/ml)	Up to 6	SRμCT HIST	Groups 3 and 5 presented higher BIC and BV compared with groups 1, 2, 4 and 6
Stadlinger et al.[31] (2008b)	10 female and 10 male minipigs (12 months old)	Group 1: Ti + CI Group 2: Ti + CI + CS Group 3: Ti + CI + CS + BMP-4	CS from bovine trachea CI from bovine skin	24	HIST	Group 2 presented higher BIC compared with groups 1 and 3
Schliephake et al.[32] (2009)	10 female dogs (NA)	Group 1: uncoated smooth Ti Group 2: uncoated rough Ti Group 3: Ti + RGD peptide Group 4: Ti + CI Group 5: Ti + CI + CS Group 6: Ti + CI + CS + BMP-2	CI of porcin origin	Up to 12	Histology HIST	Group 5 presented higher BIC and BV/TV compared with group 1, but comparable with groups 3, 4 and 6
Stadlinger et al.[33] (2009)	10 female and 10 male minipigs (12 months old)	Group 1: uncoated Ti Group 2: Ti + CI + CS low dose Group 3: Ti + CI + CS high dose	CS from bovine trachea (Group 2: 50 μg/mg) (Group 3: 500 μg/mg) CI from bovine skin (4 mg/ml)	Up to 8	Histology HIST RFA	Group 2 and 3 presented higher BIC and BV/TV compared with group 1 Comparable ISQ among all groups

Table 1 (*Continued*)

Authors (year)	Study subjects (Mean age)	Study groups	Collagen and chondroitin sulfate form (concentration)	Follow-up (weeks)	Analysis methods	Outcome
Stadlinger et al.[34] (2012)	10 female and 10 male minipigs (12 months old)	Group 1: uncoated Ti Group 2: Ti + CI Group 3: Ti + CI + CS low dose Group 4: Ti + CI + CS high dose Group 5: Ti + CI + HYA high dose Group 6: Ti + CI + HYA low dose	CS from bovine trachea (Group 3: 50 μg/mg) (Group 4: 500 μg/mg) CI from bovine skin (2 mg/ml)	Up to 8	Histology HIST	Group 3 presented higher BIC compared with the other groups Comparable BVD and ISQ among all groups
Stadlinger et al.[35] (2013)	224 female rats (6 months old)	Group 1: Sham Group 2: Sham + conditioned Ti Group 3: OVX Group 4: OVX + conditioned Ti Group 5: OVX + CI + CS Group 6: OVX + simvastatin Group 7: OVX + zoledronic acid	CS from bovine trachea (50 μg/mg) CI from bovine skin (1 mg/ml)	Up to 4	HIST Micro-CT Removal torque	Group 5 presented lower BIC, BV/TV, and BMD compared with groups 1, 2, 4, 6 and 7, and comparable with group 3 Removal torque was higher in group 5 compared with groups 3, 4 and 6
Dudeck et al.[36] (2014)	30 female rats (NA)	Group 1:OVX + EFD + Ti Group 2: OVX + EFD + CI + CS Group 3: OVX + ED + Ti Group 4: OVX + ED + CI + CS Group 5: OVX + GD + Ti Group 6: OVX + GD + CI + CS	CS from bovine trachea (10% mass) CI from bovine skin (NA)	4	SRμCT SNI Histology HIST	Groups 4 and 6 presented higher NBF and affinity index compared with groups 1, 2, 3 and 5
Korn et al.[37] (2014)	6 female minipigs (45 months old)	Group 1: uncoated Ti Group 2: Ti +CI + CS Group 3: Ti + HYA	CS from porcine trachea (250 μmol/l) CI from rat tail (1 mg/ml)	Up to 8	Histology HIST	Group 2 and 3 presented higher BV/TV compared with group 1 BIC among all the groups was comparable
Liu et al.[38] (2014)	24 sheep (2.5 to 3 months old)	Group 1: uncoated Ti Group 2: Ti + HA Group 3: Ti + CI + CS Group 4: Ti + HA + CI + CS	CS from bovine trachea (1 mg/ml) CI from rat tail (4 mg/ml)	Up to 12	Micro-CT HIST Pull-out test	BMC, BMD, and BVF among all the groups were comparable Group 4 presented higher strength of fixation compared with groups 1, 2 and 3
de Barros et al.[39] (2015)	6 male dogs (NA)	Group 1: uncoated Ti Group 2: Ti + CII + CS Implants were placed with and without a bone defect (0.5, 1, or 2 mm in width and 5 mm in depth)	CS from porcine trachea (0.1 mg/ml) CII from chicken sternal cartilage (1 mg/ml)	Up to 8	Fluorochrome labeling Histology HIST	Group 2 presented higher mineralization compared with group 1 Group 2 presented higher NBF and BIC compared with group 1 in gapless and 0.5 mm gaps
Hydroxyapatite implants with collagen and chondroitin sulfate						
Schneiders et al.[40] (2008)	60 male rats (NA)	Group 1: HA + CI Group 2: HA + CI + CS	CI (2.5 wt%) CS (5 mg/g)	Up to 4	Histology HIST	Group 2 presented higher BIC and NBF compared with group 1
Schneiders et al.[41] (2009)	14 female sheep (NA)	Group 1: HA + CI Group 2: HA + CI + CS	CI (2.5 wt%) CS (5 mg/g)	12	Histology HIST CT scan IHC EHC	Group 2 presented higher BIC and NBF compared with group 1

APC, anodic plasma–chemical surface modification; BIC, bone-to-implant contact; BMC, bone mineral content; BMD, bone mineral density; BMP, bone morphogenetic protein; BVD, bone volume density; BVF, bone volume fraction; BV/TV, bone volume density; CaP, calcium phosphate; CI, collagen type I; CII, collagen type II; CS, chondroitin sulfate; ED, estradiol-rich diet; EFD, estrogen free diet; EHC, enzyme histochemistry; GD, genistein-rich diet; HA, hydroxyapatite; HIST, histomorphometry; HYA, non-sulfated hyaluronan; IHC, immunohistochemistry; ISQ, implant stability quotient; Micro-CT, microcomputed tomography; NA, not available; NBF, new bone formation; OVX, ovariectomized; RFA, resonance frequency analysis; RGD, arginine–glycine–aspartate; SNI, scanning nanoindentation; SRμCT, synchrotron radiation micro-computed tomography; TGF, transforming growth factor; Ti, titanium; Zr, zirconia.

Table 2. Characteristics of the implants used.

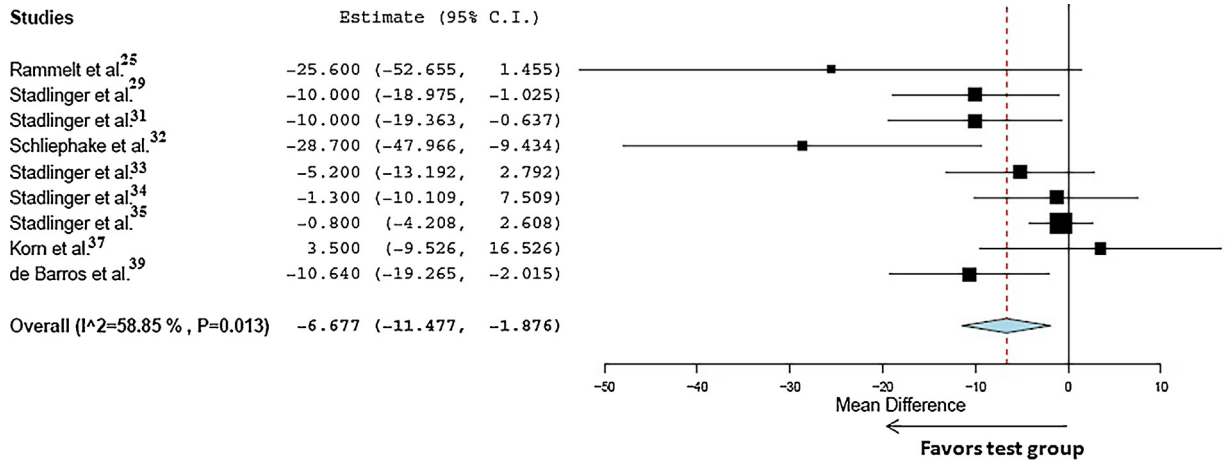
Authors	Number and material of implants	Implant dimensions (D × L, mm)	Location of implant placement	Implant shape	Implant surface characteristics
Titanium implants with collagen and chondroitin sulfate coated surfaces					
Schliephake et al.[24] (2005)	Ti (NA)	4 × NA	Mandible	Screws (modified)	Smooth
Rammelt et al.[25] (2006)	72 Ti	0.8 × NA	Tibia	Pins	Smooth
Rammelt et al.[26] (2007)	24 Ti	5.5 × NA	Tibia	Screws	Rough (SB)
	24 Ti	4 × NA	Tibia	Cylinder	Rough (SB)
Ferguson et al.[27] (2008)	90 Ti and 18 Zr	4.2 × 8	Pelvis	Cylinder	Rough (SB + AE)
Langhoff et al.[28] (2008)	93 Ti and 18 Zr	NA	Pelvis	Cylinder	Rough (SB + AE)
Stadlinger et al.[29] (2007)	120 Ti	4.25 × 12	Mandible	Cylinder (modified)	Rough (SB)
Stadlinger et al.[30] (2008a)	48 Ti	4 × 12	Mandible	Cylinder (modified)	Rough (SB)
Stadlinger et al.[31] (2008b)	120 Ti	4.25 × 12	Mandible	Cylinder (modified)	Rough (SB)
Schliephake et al.[32] (2009)	Ti (NA)	4 × NA	Mandible	Screws (modified)	Smooth Rough (AE)
Stadlinger et al.[33] (2009)	60 Ti	4.5 × 9.5	Mandible	Cylinder (modified)	Rough (SB + AE)
Stadlinger et al.[34] (2012)	120 Ti	4.5 × 9.5	Maxilla	Cylinder (modified)	Rough (SB + AE)
Stadlinger et al.[35] (2013)	224 Ti	1.7 × 3	Tibia	Screw	Rough (SB + AE)
Dudeck et al.[36] (2014)	Ti (NA)	0.8 × NA	Tibia	Pins	Smooth
Korn et al.[37] (2014)	36 Ti	5 × 15	Mandible	Screws	Rough (SB + AE)
Liu et al.[38] (2014)	96 Ti	3 × 3	Spine (L4–L5)	Pedicle screws	Rough (SB)
de Barros et al.[39] (2015)	48 Ti	3.5 × 9.5	Mandible	Cylinder	Rough (SB + AE)
Hydroxyapatite implants with collagen and chondroitin sulfate					
Schneiders et al.[40] (2008)	60 HA	2 × 6	Tibia	Cylinder	NA
Schneiders et al.[41] (2009)	14 HA	2.5 × 3, with an 8-mm central hole	Tibia	Cylinder	NA

AE, acid-etched; D, diameter; L, length; NA, not available; SB, sand-blasted; Ti, titanium; Zr, zirconia.

the five studies ($Q = 7.5$, $P = 0.11$). The random-effects model showed that the combined NBF in the test group did not differ significantly from that in the control group (mean difference = −3.9, $P = 0.17$) (Fig. 3).

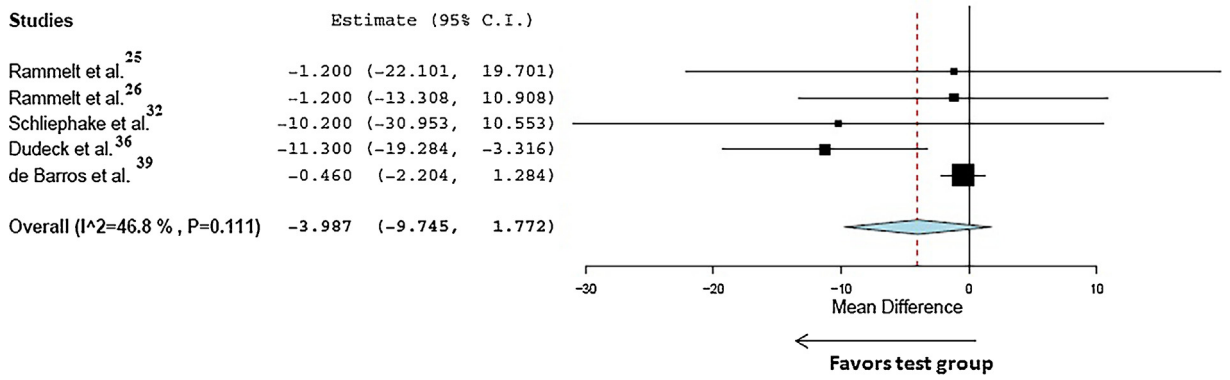
Quality assessment

Eleven studies reported an adequate method of randomization or method of allocation concealment[26,28–31,33,34,36–39]. Three studies conducted blinding of examiners with regard to the assessment of osseointegration and/or bone mineralization[33,39,41]. The number of subjects at baseline and at the final examination was described in 16 studies (Fig. 4)[24–26,28–37,39–41].



Study	Control			Test			Weights
	Mean	SD	Total	Mean	SD	Total	
Rammelt et al.[25]	63.9	56.8	18	89.5	14.27	18	2.758%
Stadlinger et al.[29]	45	7.24	5	55	7.24	5	12.510%
Stadlinger et al.[31]	30	15.3	21	40	18.4	29	12.044%
Schliephake et al.[32]	37.7	13.3	5	66.4	17.5	5	4.853%
Stadlinger et al.[33]	62.7	8.65	9	67.9	8.65	9	13.755%
Stadlinger et al.[34]	62.1	9.17	9	63.4	9.32	8	12.713%
Stadlinger et al.[35]	20.6	2.4	6	21.4	3.8	7	19.992%
Korn et al.[37]	44.7	11.2	5	41.2	10.7	6	8.431%
de Barros et al.[39]	54.90	13.32	24	65.54	16.95	24	12.943%
Total			102			111	

Fig. 2. Forest plot presenting the mean difference (MD) for bone-to-implant contact between the control and test groups.



Study	Control			Test			Weights
	Mean	SD	Total	Mean	SD	Total	
Rammelt et al.[25]	35.7	30.3	18	36.9	33.6	18	6.561%
Rammelt et al.[26]	18.9	10.6	6	20.1	10.8	6	15.411%
Schliephake et al.[32]	36.2	18.4	5	46.4	14.9	5	6.642%
Dudeck et al.[36]	30.4	9	5	41.7	1.4	5	25.067%
de Barros et al.[39]	8.85	2.98	24	9.31	3.18	24	46.319%
Total			58			58	

Fig. 3. Forest plot presenting the mean difference (MD) for new bone formation between the control and test groups.

Discussion

This study assessed the efficacy of collagen–CS matrix incorporation into implant surfaces in enhancing osseointegration. Thirteen of the studies included (72%) reported that implants coated with a collagen–CS matrix presented higher NBF, BIC, and/or BV/TV[24,25,29–34,36,37,39–41]. The strength of this observation was supported by meta-analysis results.

Quantitative analysis has been used to pool data from human clinical studies, and it has been reported that this is applicable in animal research as well[47–50]. In this context, these results appear persuasive enough to conclude that implant surface coating with collagen–CS matrix enhances osseointegration. However, it would be difficult to reproduce these experimental results in a clinical setting for a number of reasons. First, establishing the dosage formulation of collagen–CS matrix that yields the most predictive outcome (improving NBF and/or BIC) would be challenging. For instance, de Barros et al. dip-coated implant surfaces with a solution of type II collagen from chicken sternal cartilage (1 mg/ml) and 0.1 mg/ml CS from porcine trachea (70% of chondroitin-4-sulfate and 30% of chondroitin-6-sulfate)[39], whereas Rammelt et al. used biomimetic fibrillogenesis to fix CS from bovine trachea (10 mass % chondroitin-4-sulfate) in a matrix of acid-soluble bovine skin type I collagen (1 mg/ml)[25,26]. Second, the final amount of matrix on the implant surface also varied among the studies included. For example, the final amount of collagen matrix on the implant surface ranged between 10 and 15 $\mu g/cm^2$ in the study by Rammelt et al.[26], whereas the collagen adsorbed into the implant surfaces ranged between 45 and 55 $\mu g/cm^2$ in the study by Stadlinger et al.[29]. This highlights the lack of agreement regarding the dosage and formulation of collagen–CS matrix in the studies included, which need to be further optimized.

There was also a lack of standardization in the selection of implants for the control groups in the studies included. For example, in the study by Schliephake et al., machined surface titanium screws were used as controls[24], whereas Ferguson et al. used cylindrical titanium implants with rough surfaces (sand-blasted and acid-etched) as controls[27]. From a clinical perspective it may be argued that implant surface roughness itself is a key factor that influences osseointegration. It is well established that rough surface implants positively influence osteogenic cell proliferation, attachment, and differentiation compared with machined surface implants[51,52]. Therefore, its contribution to bone formation around implants (regardless of whether collagen–CS matrix is used or not) cannot be ignored.

It is proposed that additional studies with the following groups are needed: (1) machined surface implants without collagen–CS matrix coating (control group 1); (2) rough surface implants without collagen–CS matrix coating (control group 2); (3) machined surface implants with collagen–CS matrix coating (test group 1); and (4) rough surface implants with collagen–CS matrix coating (test group 2). From the literature reviewed, only Schliephake et al. used a similar protocol to that proposed here[32]. Therefore, further well-designed studies are needed to assess the contribution of collagen–CS matrix itself to the promotion of osseointegration.

It is pertinent to mention that the follow-up period among the experimental studies included was relatively short (up to 24 weeks)[24–41]. It remains unclear whether the addition of collagen–CS matrix in implant surfaces in a clinical scenario would increase NBF and improve the long-term success of dental implants. Furthermore, since all studies included were performed in animals, it remains debatable whether or not implant surfaces coated with a collagen–CS matrix would enhance NBF among patients with confounding parameters that may influence healing and impair osseointegration (such as stress, poor oral hygiene, tobacco habits, and poorly controlled diabetes mellitus). Moreover, it would be challenging to extrapolate these experimental findings to human trials due to several factors, such as clinical significance, predictability, and practicability. Further long-term, randomized, controlled clinical trials based on sample sizes determined by a power analysis are warranted. Furthermore, the most relevant follow-up duration that could yield reliable results remains to be determined.

In conclusion, on experimental grounds, the incorporation of collagen–CS matrix into implant surfaces appears to promote osseointegration. From a clinical perspec-

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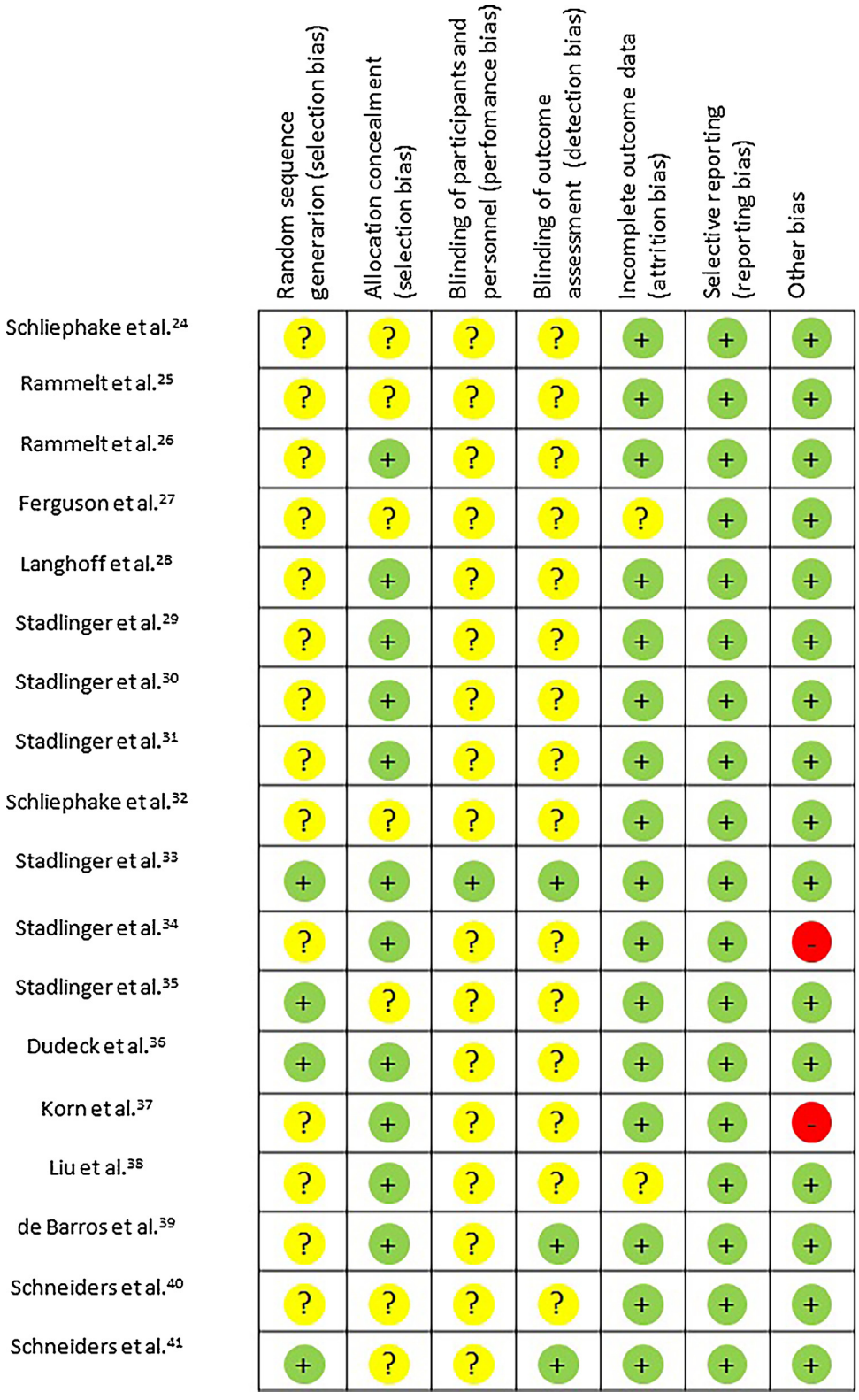

Fig. 4. Methodological quality of the studies included.

tive, the results from animal models support phase I studies in healthy humans.

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Competing interests

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Ethical approval

Not required.

Patient consent

Not required.

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