Int. J. Oral Maxillofac. Surg. 2017; xxx: xxx–xxx
https://doi.org/10.1016/j.ijom.2017.10.010, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Meta-Analysis
Dental Implants

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

S. V. Kellesarian[1], V. R. Malignaggi[2], T. V. Kellesarian[2,3], H. Bashir Ahmed[4], F. Javed[1]

[1]Department of General Dentistry, Eastman Institute for Oral Health, University of Rochester, Rochester, New York, USA; [2]Department of General Dentistry, Dental School, Santa Maria University, Caracas, Venezuela; [3]College of Health Sciences, Barry University, Miami Shores, Florida, USA; [4]Private Dental Practice, Doha, Qatar

S. V. Kellesarian, V. R. Malignaggi, T. V. Kellesarian, H. Bashir Ahmed, F. Javed: Does incorporating collagen and chondroitin sulfate matrix in implant surfaces enhance osseointegration? A systematic review and meta-analysis. Int. J. Oral Maxillofac. Surg. 2017; xxx: xxx–xxx.

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.

Accepted for publication 18 October 2017

0901-5027/000001+011

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