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Review

Laminin coatings on implant surfaces promote osseointegration: Fact or fiction?

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ABSTRACT

To our knowledge from indexed literature, the role of laminins in the expression of osteogenic biomarkers and osseointegration enhancement has not been systematically reviewed. The aim of the present systematic review was to assess the role of laminin coatings on implant surfaces in promoting osseointegration. To address the focused question, "Do laminin coatings on implant surfaces influence osseointegration?", indexed databases were searched from 1965 up to and including November 2015 using various combination of the following keywords: "Bone to implant contact"; "implant"; "laminins"; and "osseointegration". Letters to the Editor, case-reports/case-series, historic reviews, and commentaries were excluded. The pattern of the present systematic review was customized to primarily summarize the pertinent data. Nine studies were included. Six studies were prospective and were performed in animals and 5 studies were *in vitro*. Results from 8 studies showed that laminin coatings enhanced new bone formation around implants and/or bone-to-implant contact. One study showed that laminin coated implants surfaces did not improve osseointegration. On experimental grounds, laminin coatings seem to enhance osteogenic biomarkers expression and/or osseointegration; however, from a clinical perspective, further randomized control trials are needed to assess the role of laminin coatings in promoting osseointegration around dental implants.

Contents

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1. Introduction

Osseointegration plays an essential role in the long-term success and survival of implants. A variety of therapeutic protocols have been proposed in an attempt to enhance bone formation around implant surfaces. These include the use of growth factors (such as the platelet derived growth factor, basic fibroblast growth factor, insulin-like growth factor-I and bone morphogenetic protein 2) and placement of osteogenic coatings on implant surfaces (Alghamdi et al., 2013; Chang et al., 2012; de Jonge et al., 2010; Javed, Vohra, Zafar, & Almas, 2014; Javed et al., 2015, 2016; Lan, Wang, Wang, Wang, & Cheng, 2006; Nagayasu-Tanaka et al., 2016; Yoo et al., 2014). It has also been reported that modifications in topography and the surface chemistry enhances cell attachment, proliferation and expression of osteogenic genes and angiogenic factors, compared to turned pure titanium surfaces (Wang et al., 2015; Xuereb, Camilleri, & Attard, 2015; Yeo, 2014). To date, only a limited number of studies (Bougas, Stenport, Currie, & Wennerberg, 2011; Bougas, Jimbo et al., 2012; Bougas, Stenport, et al., 2012; Bougas et al., 2013, 2014; Kang et al., 2013; Min et al., 2013; Schwartz-Filho et al., 2012; Yeo et al., 2015) have investigated the role of laminins coatings on implant surfaces on osseointegration and new bone formation (NBF) around implants.

Laminins are glycoproteins and major structural components in the basal lamina of most cells and organs tissues, including brain, skeletal muscle, and peripheral nerves. (Rohde, Wick, & Timpl, 1979; Timpl et al., 1979) Laminins present a heterotrimeric structure with 3 chains (α, β and γ), forming a cross-like structure. Laminin α2 chains present a large globular (LG) domain-like module capable to bind cell transmembrane molecules, including integrins, syndecans and dystroglycans. (Timpl et al., 2000) This binding property confers to laminins biological activities, including cell adhesion, differentiation and migration, angiogenesis and tumor metastasis (Colognato and Yurchenco, 2000; Suzuki, Yokoyama, & Nomizu, 2005). Twelve different heterotrimers have been identified and numbered in the order discovered. (laminin 1 to laminin 12). (Aumailley et al., 2005; Burgeson et al., 1994)

The effect of different laminin heterotrimers and isoforms on osseointegration has been reported (Kang et al., 2013; Yeo et al., 2015). Results from *in vitro* studies have shown that laminin-1 stimulates osteoblastic alkaline phosphatase (ALP) production (Vukicevic, Luyten, Kleinman, & Reddi, 1990) and osteoprogenitor cells proliferation through an integrin β1-dependent cell attachment effect (Roche, Goldberg, Delmas, & Malaval, 1999). *In vitro* studies (Bougas et al., 2011; Bougas, Stenport et al., 2012) have shown that laminin-1 increases the precipitation of calcium phosphate (CaP). Likewise, results from other *in vivo* studies (Bougas, Jimbo et al., 2012; Bougas et al., 2013, 2014) have also reported that laminin-1 coatings improve osseointegration around implants. Laminin-2 derived peptides have been studied as novel therapeutic agents due to their smaller molecular weight and lower antigenicity. Laminin-2-P3 and Laminin-2-LG3 have been reported to enhance bone cell function *in vitro* (Kang et al., 2013; Min et al., 2013; Yeo et al., 2015) and to induce faster osseointegration around titanium implants *in vivo*. (Kang et al., 2013; Yeo et al., 2015) Moreover, *in vitro* studies have shown that Laminin-5 enhances epithelial cell attachment and spreading, and hemidesmosome assembly around titanium discs (El-Ghannam, Starr, & Jones, 1998; Tamura et al., 1997; Werner et al., 2009). It is therefore hypothesized that laminin coatings play a role in enhancing osseointegration. However, controversial results have been also reported regarding laminins effect on implant osseointegration. Schwartz-Filho et al. (2012) reported significantly higher levels of osteoblastic and osteoclastic markers, but no significant difference in bone apposition around implants coated with laminin-1 compared to control.

From the currently available evidence, there seems to be a relationship between laminin coatings and osseointegration of implants. However, to our knowledge from indexed literature, the role of laminins in the expression of osteogenic biomarkers and osseointegration enhancement has not been systematically reviewed. Therefore, the aim of the present systematic review was to assess the role of laminin coatings on implant surfaces in promoting osseointegration.

2. Methods

2.1. Focused question

The addressed focused question was "Do laminin coatings on implant surfaces influence osseointegration?"

2.2. Eligibility criteria

The eligibility criteria were as follows: (a) clinical studies, (b) experimental studies (*in-vivo* and *in-vitro*), (c) inclusion of a control group (osteogenic biomarkers expression and/or osseointegration around non-coated implants); and (d) intervention: effect of laminin coating on osseointegration around implants. Letters to the Editor, historic reviews, commentaries, case-series and case-reports were excluded.

2.3. Literature search protocol

PubMed/Medline (National Library of Medicine, Washington, DC), EMBASE, Scopus, Web of knowledge and Google-Scholar databases were searched from 1965 up to and including February 2016 using various combination of the following keywords: (a) laminins + osseointegration; (b) laminins + implants; (c) laminins + implants + osseointegration; (d) bone to implant contact + laminins; (e) bone to implant contact + laminins + osseointegration. Search titles and abstracts were initially screened by one author (SVK) to exclude articles that were clearly outside the scope of the review. The remaining titles and abstracts of studies identified using the above-described protocol were screened by two authors (FJ and SVK) and checked for agreement. Full-texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. Reference lists of potentially relevant original and review articles were hand-searched to identify any studies that could have remained unidentified in the previous step. Once again, the articles were checked for disagreement via discussion among the authors. The initial search yielded 176 studies. One hundred and sixty seven studies that did not abide by the eligibility criteria were excluded. In total, 9 articles (Bougas et al., 2011; Bougas, Jimbo et al., 2012; Bougas, Stenport et al., 2012; Bougas et al., 2013, 2014; Kang et al., 2013; Min et al., 2013; Schwartz-Filho et al., 2012; Yeo et al., 2015) were included and processed for data extraction (Fig. 1).