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Review

Systematic review of wound healing biomarkers in peri-implant crevicular fluid during osseointegration

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ABSTRACT

Objective: To quantify and characterize the role of biomarkers in peri-implant crevicular fluid (PICF) at each stage of healing during osseointegration.
Design: This systematic review was performed in accordance with PRISMA guidelines using several databases: MedLine (PubMed), Embase, ISI Web of Science, Scopus, and Cochrane Library. Medical subject headings and their indexers were used with no other limitations until December 2017. The dataset was extended with relevant papers from the reference lists of selected papers and from the gray literature. Data was summarized for study objectives, patient demographics, methods used to analyze PICF, biomarker concentrations, results and main findings. Methodologic quality of each included study was assessed using the checklist created by Downs and Black.
Results: Electronic search resulted in 1698 articles. After excluding the duplicates, reading titles, abstracts and reference list reviews 30 prospective studies with longitudinal follow-up were selected. In total, 52 different biomarkers were identified. The most studied cytokines were interleukin (IL)-1, IL-1β, tumor necrosis factor alpha (TNF-α), and nitric oxide (NO). The earliest PICF specimens were collected immediately after implantation, and the latest at 16 weeks prior to occlusal loading. 36 biomarkers were quantified during week 1, 49 between day 10 and week 6, and 49 between weeks 8 and 12. Only 5 articles received good quality ratings.
Conclusion: The mechanism by which inflammatory and bone biomarkers are released during osseointegration has not yet been identified. However, some hypotheses based on immune-modulated reactions are being explored to investigate early and asymptomatic implant failures. Given the available clinical studies, it was not possible to further explore the performance of all biomarkers already analyzed and to extrapolate their results to propose a consultable data system based on release volume or concentration because of clinical study and data heterogeneity.

1. Introduction

Successful rehabilitation after dental implants installation requires maximal bone-implant interaction after osseointegration, wherein osteoinductive and osteoconductive processes (Albrektsson & Johansson, 2001) generate the molecular and cellular events of neoformation and bone remodeling (Trindade, Albrektsson, & Wennerberg, 2015a; Trindade, Albrektsson, & Wennerberg, 2015b). The osseointegration process involves homeostasis, formation of granulation tissue, bone formation, and remodeling (Bosshardt, Chappuis, & Buser, 2017). Bone homeostasis is mainly driven by the periosteum and osteocytes activity at the tissue and cellular level. The periosteum plays an important role for implants with subcrestal positioning, such as those with the recently developed morse taper connections. In cases of guided bone regeneration therapy, the periosteal cells can also differentiate into osteoblasts contributing to the radial bone growth by continuously producing mature osteoblasts from periosteal progenitor cells, as observed during healing of long bone fractures (Roberts et al., 2015). Osteocytes cells are terminally differentiated osteoblasts that regulate the mineralization and form the connective dendritic processes (Bonewald, 2011;

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Insua, Monje, Wang, & Miron, 2017). The osteocytes are key regulators of bone homeostasis because they release signaling factors to recruit osteoclasts in bone remodeling sites, and can inhibit osteoblast activity (Bonewald, 2011; Insua et al., 2017). Thus, successful implant osseointegration requires *de novo* bone formation on the surface of the implant through a continued recruitment and migration of differentiating osteogenic cell to the implant site during the contact osteogenesis. This dynamic process operates in an identical fashion to remodeling bone surfaces occupied by a cement line matrix. Simultaneously, the distance osteogenesis occurs together with contact osteogenesis in every endosseous healing site (Davies, 2003).

Even though well-established surgical implant protocols can yield ≥95% success rates (Buser, Sennerby, & De Bruyn, 2017), early failures are still a great concern among clinicians and researchers (Albrektsson, Chrcanovic, Östman, & Sennerby, 2017; Alsaadi, Quirynen, Komárek, & Van Steenberghe, 2007; Chrcanovic, Kisch, Albrektsson, & Wennerberg, 2016; Koka & Zarb, 2012; Manzano et al., 2016). These early failures occur without a known biological mechanism and there appears to be no evidence that primary infection is the major causative factor for marginal bone resorption (Albrektsson, Buser, & Sennerby, 2012; Qian, Wennerberg, & Albrektsson, 2012). One possible reason for early failures might be that the bone healing after implant insertion is impaired by local and systemic factors, resulting in failure to establish an intimate bone-to-implant contact (Alsaadi et al., 2007; Chrcanovic et al., 2016). Another hypothesis states that peri-implant tissue around failing implants may contain cytokines with the potential to regulate the activity of osteoclasts, which lead to speculations about clinical interventions based on accessible targets for local therapies with cytokine modulators (Konttinen et al., 2006). Some studies hypothesized that early dental failures could be related to inflammatory reactions in the peri-implant tissues caused by particles derived from the dental implants surface (Franchi et al., 2004; Goodman, 2007; Kumazawa et al., 2002). These particles can be released by implant exposure to therapeutic corrosive substances and/or mechanical procedures (e.g. surgical insertion; micro- movements between contacting surfaces at implant connections), that result in a host-immune response (Noronha Oliveira et al., 2018). Finally, Albrektsson et al. (2014) proposed a model in which implant osseointegration is a long-term equilibrium between host immune cells and bone biomaterials, and the failures are related to healing *dis-balance (*Albrektsson et al., 2014). This model was later relabeled as the *Foreign Body Reaction* hypothesis, which states that the bone microenvironment responds to dental implants as foreign bodies. The latter initiates an immune-modulated reaction, cell signaling and complement system activation triggering an inflammatory healing reaction (Trindade et al., 2015a, 2015b; Trindade, Albrektsson, Tengvall, & Wennerberg, 2016).

Trindade et al. (2018) recently found evidence for the involvement of the immune system during the process of osseointegration around titanium implants (TI) in an animal pilot study. In this study, histological gene expression analyses indicated that the immune system activated displays type 2 inflammation that likely guides the host-biomaterial relationship. They found that the TI suppress bone resorption, favoring the bone formation and generating an immunological host reaction. The bone deposition on the implant surface is then initiated to isolate the implant from the bone marrow space, resulting in an accidental clinical osseointegration. After 10 days, the sites with TI had an initial bone formation and presented an increase in arginase-1, indicating a greater activation of type 2 macrophages (M2-macrophages) and cells of the innate responses suggesting an activation of the immune system. After the inflammatory period, at 28 days, TI showed a more active and organized bone remodeling and formation. In addition, the expression of factors related to M1- and M2- macrophages, leucocytes, type 2 innate lymphoid cells, neutrophils, and complement system components indicated a prolonged activation of the innate immune system (Trindade et al., 2018). The role of immuno-biological responses during osseointegration was also highlighted in a recent *in vitro study* by Ma et al. (2018) describing the effects of the implant surface on immune cells and bone mesenchymal stem cells (bMSCs). These authors suggested that the alteration of the surface nanostructure can control the inflammatory response of the macrophages. The macrophages tend to facilitate the osteogenic behavior of bMSCs and attract fewer inflammatory cells, improving the clinical performance of the implants by manipulating the balance of bone regeneration/absorption. Their main results included increases in secretion of receptor activator of nuclear factor-B ligand (sRANKL) and macrophage colony-stimulating factor (M-CSF) that may result from increased concentrations of IL-1β and IL-6, since increased osteoprotegerin (OPG) and OPG/sRANKL ratios are induced by transforming growth factor beta (TGF-β) alone or in combination with bone morphogenetic protein (BMP)-2. These findings indicate that the formation of osteoclasts can be induced by immunological factors secreted by bMSCs. Hence, Ma et al. stated that understanding and monitoring the profiles of cytokines secreted by macrophages and the retroregulative cytokines released by bMSCs is important, because they can provide a framework for systematically analyzing and predicting the performance of an implant (Ma et al., 2018).

In recent years, the correlation between clinical indicators of peri-implant health monitoring and marginal bone loss was questioned (Albrektsson et al., 2012; Lin, Kapila, & Wang, 2017; Qian et al., 2012; Sanz & Chapple, 2012). Common periodontal indices such as bleeding on probing and probing depth are not always a reliable tool for assessing peri-implant marginal soft- and hard-tissue conditions (Albrektsson et al., 2012; Coli, Christiaens, Sennerby, & Bruyn, 2017). Healthy peri-implant mucosa can show an increase of probing pocket depth over time (≥4 mm), and is not necessarily associated with bone loss or disease. Likewise, bleeding on probing does not always indicate the presence of acute inflammation in the peri-implant mucosa, but may reflect the nature of the scar tissue–implant contact, as the absence of bleeding on probing does not always appear to be a predictor of future stability (Coli et al., 2017). In an attempt to improve the methodology to evaluate the inflammatory status of gingival tissues, biochemical analysis of gingival crevicular fluid (GFC) are being done in addition to the standard clinical tests. The collection of crevicular fluid enables the measurement of biomarkers for periodontal diseases. They are secreted products of immune cells and represent the innate immune response against bacterial pathogens and danger signals (Bostanci & Belibasakis, 2018). These evaluations may be performed in peri-implant tissue to analyze the biomarkers such as cytokines, proteins, and multifunctional peptides function as intercellular regulatory factors locally and systemically present in peri-implant crevicular fluid (PICF). These biomarkers modulate inflammation intensity, foreign body reaction, cellular organization, healing, and disease pathogenesis. During early bone healing, this immunologically-driven process is proposed to be related primarily to osteoconduction (Albrektsson & Johansson, 2001; Chang, Lang, & Giannobile, 2010; Trindade et al., 2015a, 2015b).

Biomarkers are fundamental to the intercellular interactions and cellular activation that are needed to re-establish tissue bioequivalence (Stow & Murray, 2013; Stow et al., 2009). They remain in the tissue microenvironment for various lengths of time and are present in PICF. Many researchers have studied PICF seeking to find specific markers related to pathologic inflammation, failed bone repair, and failed implantation. Biomarkers from the peri-implant microenviroment have been quantified to develop early diagnostic techniques for peri-implant disease. Previous systematic reviews (Duarte et al., 2016; Faot et al., 2015; Kaklamanos & Tsalikis, 2002) have identified possible biomarker uses and relationships to pathologic processes. These reviews aggregated data from patients with osseointegrated implants, patients with systemic or local disease, and healthy controls. In 2002, Kaklamanos and Tsalikis (2002) called for a consensus to define and describe clinical conditions and tissue status based on PICF biomarkers to monitor and predict peri-implant tissue response. A subseqeuent study by Faot et al. (2015), identified IL-1β and TNF-α as pro-