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Cytokines and Peri-Implant Disease

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Abstract

The aim of this review was to summarize data from studies making inquiries on levels of the cytokines in pathogenesis of peri-implant diseases. Here we reviewed the recent developments on IL-1β, IL-10, IL-17, IL-21, and IL-33. We highlighted recent advances during the last few years in this area and discussed their roles in immune regulation in patients with peri-implant disease.Our results revealed that identifying the levels of these cytokines (IL-1β, IL-10, IL-17, IL-21, and IL-33) may help to predict the diagnosis of peri-implant diseases. From a safety perspective, this study emphasized the need to consider the impact of these interleukin on peri-implant diseases.

Keywords: Peri-implant diseases, cytokines, interleukins

Introduction

Dental implantation is a surgical process of alloplastic material insertion into the hard and soft tissues of maxillary and mandibular jaws (Petkovic-Curcin *et al.*, 2011). The immune reaction of organism against any artificial material into the body is going to protect the organism against pathogens and injuries, and these reactions will lead to complete recovery of the tissues and accepting implants or break the implant functionality and cause implant failure, so that, in worst conditions the implant should be removed (Petkovic-Curcin *et al.*, 2011; Kondyurina & Kondyurin, 2020). Peri-implant lesions have shown to contain a wide range of inflammatory cell infiltrate, with greater proportions of plasma cells, neutrophils and macrophages (Schincaglia *et al.*, 2016).

Cytokines are small messenger proteins which are mostly secreted by immune cells and act as key modulators of immune response by playing a strategic role in differentiation, maturation, and activation of various cells types. (Lipiäinen *et al.*, 2015; Su *et al.*, 2012) Depending on specific local environments, cytokines exhibit

either pro-inflammatory effects or anti-inflammatory effects or both (Su *et al.*, 2012).

Pro-inflammatory cytokines are immune-regulatory cytokines that promote inflammation (Proinflammatory cytokines, 2020). They are mainly produced by activated macrophages and involved in up-regulation of inflammatory process. Major pro-inflammatory cytokines include IL-1β, IL-6, and TNF-α (Proinflammatory cytokines list, 2020). The anti-inflammatory cytokines are a sequence of immune-regulatory molecules that control the Pro-inflammatory response. The typical anti-inflammatory cytokines are interleukin (IL)-1 receptor antagonist, IL-4, IL-10, IL-11, and IL-13 (Anti-inflammatory cytokines, 2020). In order to maintain health, there should be a balance between pro-inflammatory and anti-inflammatory cytokines (Inflammatory cytokine, 2020). Imbalances between these two usually obstruct the resolution of inflammation and, instead, lead to tissue destruction (Duarte *et al.*, 2016). Inflammatory cytokines can perform as a predictive and preventive biological tool as well (Farhad *et al.*, 2019).

The expression of cytokines is affected by genetic, epigenetic, microbiota heterogeneity and environmental factors (Teixeira *et al.*, 2016). Peri-implant mucositis and peri- implantitis are two main inflammatory processes affecting tissues around the functional dental implant and due to inflammatory disorders, the process may cause implant loss. Nevertheless, evaluating the inflammatory cytokine levels could be a tool for early diagnose, prevention and therapy of peri-implant disease (Severino *et al.*, 2016).

In this sense, saliva is an abundant biological fluid and it's used as a diagnostic tool for a variety and range of diseases. More than 3000 proteins and peptides have been characterized by recent proteomic approaches in human saliva involved in different biological functions in the oral cavity (Bhattarai *et al.*, 2018; Ventura *et al.*, 2018). Thus, salivary cytokines could be important to analyze the changes in peri-implant diseases (Fonseca *et al.*, 2012). Moreover, saliva samples are easy to be collected in a noninvasive manner and at *low-price*, but in few articles, authors examined salivary biomarkers to investigate the presence and progression of the peri-implant disease (Teixeira *et al.*, 2016).

The present study was designed to determine the importance of IL-1β, IL-10, IL-17, IL-21, IL-33 as biochemical markers for early diagnosis and early prevention of peri-implant diseases.

Interleukin 1 beta (IL-1β) - IL-1β is a pro-inflammatory cytokine present in healthy peri-implant tissues in certain concentration. The progression of gingival

inflammation is due to the consequence of IL-1β and IL-6 activities, which cause a significant tissue damage by osteoclasts activation (Petkovic-Curcin *et al.,* 2011).

Interleukin 10, 17 and 21 (IL-10, IL-17 and IL-21) - IL-10 and IL-17 are among the new cytokines that have not yet been extensively investigated in prior researches (Farhad *et al.,* 2019). IL-10 is a human cytokine with potent anti-inflammatory properties. Thereby, IL-10 prevents host damaging by limiting immune response to pathogens. IL-17 is a pro-inflammatory cytokine that plays both protective and tissue destruction role in immune system. The main role of IL-17 against infection is to influence on neutrophils and activate macrophages in the infectious origin (Farhad *et al.,* 2019). The occurrence of peri-implant disease is the result of a dysregulated host immune response to periodontal bacteria. A *number* of existing studies have recently focused on presence and function of IL-17 in these diseases (Farhad *et al.,* 2019; Lira-Junior *et al.,* 2019). According to the result of a study conducted in 2014, concentrations of IL-17 reduced as a consequence of the progression of gingivitis to periodontitis means that in the presence of higher depth of dental pocket the level of IL-17 was decreased (Johnson *et al.,* 2004). In another comparative study between mucositis and peri-implantitis sites reported in 2016, a significant increase has been found in IL-21 levels in mucositis than peri-implantitis according to author's judgment that was the first study to investigate the expression of IL-21 in peri-implant disease (Teixeira *et al.,* 2016).

Interleukin 33 (IL-33) - The IL-33 is a member of the IL-1 family and plays a central role in immune responses where has recently demonstrated that the *Production of* IL-33 by induction of RANKL is *Associated* with periodontal disease. Therefore, by increasing the levels of IL-33 the tissue destruction may increase in mucositis and peri-implantitis (Severino *et al.,* 2016).

Currently, the frequent diagnostic tools for peri-implant disease are radiographic parameters and clinical signs including probing depth, bleeding on probing, suppuration, degree of implant mobility and bone loss (Duarte *et al.,* 2016). Though, it is not easy to perform all of these diagnostic methods or might not be sufficient enough to differentiate the peri-implant disease onset, activity and progression; That is why, there is a need of an investigative effort to identify the levels of different cytokines which may help to predict more accurate diagnosis, activity and progression of peri-implant disease. Particularly few studies have been carried out and explored the role of interleukins in the pathogenesis of peri-implant diseases (Farhad *et al.,* 2019).

Conclusion

The available evidence suggests that levels of certain interleukins (IL-1β, IL-10, IL-17, IL-21, and IL-33) may aid in the diagnosis and early prevention of peri-implant diseases when used in combination with other biomarkers and approaches. Consequently, further research is needed to obtain determinative results in this regard.

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