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Mechanism of action of egfs in peri-implant physiology

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Abstract

Objective: to understand the action of EGF on peri-implant behavior and what are the consequences of such interaction with the changes occurring in the prosthetic components of implant-supported dentures. **Material and Methods:** a search was done in the indexers OldMedline and Medline database, between 1980 and 2017, with the following terms in English: epidermal growth factor, osseointegration, and bone resorption. For the national literature, the indexer BBO was used. Likewise, the terms epidermal growth factor, osseointegration and bone resorption were investigated, in the same period. **Results:** recently, in terms of science, it has been found that EGFs have a role in maintaining biological distances also in peri-implant tissues. The cervical bone resorption, known as saucerization, which causes lowering of the level of the alveolar ridge is caused by the approach of the stratified squamous epithelium of the buccal mucosa, after the surgical act, to the underlying bone. **Conclusion:** the EGF mediator interacts with the receptors forming the peri-implant junctional epithelium, whose conformation approximates the bone, accelerating the resorption and provoking the saucerization. Changes in prosthetic components have been constant to fit the peri-implant behavior.

Keywords: Epidermal growth factor; Osseointegration; Bone resorption.

Introduction

Epidermal growth factor or epidermal or epithelial growth factor (EGF) is a mediator, it has the primary function of stimulating growth, differentiation and proliferation of epithelial cells. It is present in human (100 µm / mL), maternal (80 µm / mL), salivary (12 µm / mL), plasma fluid (100 µm / mL) and amniotic fluid (1 µm / mL). The Human 4 chromosome controls the production of EGF, a molecule with 53 amino acids, with a molecular weight of 6,045 daltons. It has stability even at higher temperatures. In fibroblasts, junctional epithelium and endothelial cells the EGF acts to promote cellular mitoses. However, EGF receptors are not present in the pulp tissues.[1]

EGF has been associated with carcinogenesis, by stimulating DNA synthesis and undoubted cell proliferation. It also induces osteoclastogenesis, a fact evidenced by the alteration of endochondral ossification in rats due to the deficiency of receptors for EGFs, which prevented osteoclastic action.[2,3]

In the marginal gingival tissue, facing the inner (cervical) surface of the dental element, there are three structural divisors whose dimensions are known as biological distances: average extension of the gingival sulcus (0.69 mm), mean extension of the junctional epithelium (0.97 mm); and the mean extension of the conjunctive insertion (1.07 mm).[4] When there is an invasion of these distances from a surgical or restorative procedure, or even at the periodontitis, a reabsorption of the level of the alveolar ridge at the apical direction is noted. The junctional epithelium is induced to proliferate, produces EGF, and continuous proximity to the alveolar bone crest induces a bone resorption, lowering it in the cervico-apical direction.[5]

The term saucerization is well knowing by the literature in implantology. The bone-integrated implants exhibit a cervical bone resorption around the bone margin juxtaposed to the fixation, 0.2 mm deep, being shallow, forming an open angle on their faces, assuming the shape of a saucer (saucer = English saucer hence the term embodied = saucerization).[6,7] the ulceration of the stratified squamous epithelium of the oral mucosa to expose the membrane receptors. EGF are present in saliva and in the epithelial cells begin to "shape" the formation of peri-implant junction epithelium, similar to the intact natural tooth. The approach of the peri-implant bone-integrated in the apical surface of the junction epithelium is responsible for increasing the regional concentration of EGF; and consequently the resorption of the alveolar bone crest in contact with the implant, that is, the saucerization.[1]

This work aims to review the literature on the action of EGFs on peri-implant behavior and the substantially alteration on the prosthetic components used in contemporary osseointegrated implants.

Material And Methods

This research is descriptive and exploratory, wrote through a review of narrative literature, with qualitative analysis of the results. The literature review was carried out from electronic research. The indexes OldMedline and Medlinedatabase (Figure 1) were used in between the years of 1980 and 2017, with the following terms in English: epidermal growth factor, osseointegration, and bone resorption. For the national literature, the BBO index was used (Figure

2). Likewise, the terms: epidermal growth factor, bone integration and bone resorption were investigated from 1980 to 2017. After read 64 articles, 23 articles was selected; subsequently in English, as well as, 6 in Portuguese, in addition to a book, which had a greater affinity with the proposed goal. The inclusion criteria for the articles were the aspects covered in implant-supported restorations, bone loss or resorption and its relation to the secretion of EGFs after the surgical procedure. They were taken into account: the saucerization and aspects related to the prosthetic components used and their related changes with the new peri-implant biological distances. The main focus was the studies that demonstrated studies of longevity and permanence of prosthetic abutments with platform alterations, or even bio-mechanics of abutment with cervical level saucerization, and which changes were mentioned as having a direct influence of the action of EGFs on the behavior of peri-implant tissues. Articles that did not mention a direct causal relationship between the saucerization mechanism and the action of EGFs were excluded. Other types of correlation or assumption not directly cited between re-absorption around peri-implant bone tissue were excluded, as well as changes in the biological distances promoted by periodontal diseases, occlusion forces and their resulting, lack of reverse planning, many syndromes, bone alterations promoted by medications or deleterious habits, lack of careful execution in the prosthetic phase before the placement of the fixations or theories discordant of the direct action of the EGFs and the saucerization. The searches were carried out between January 1980 and May 2017. The total number of articles obtained by this search was 64 (sixty-four). Of these, 30 (thirty) articles met the inclusion criteria.

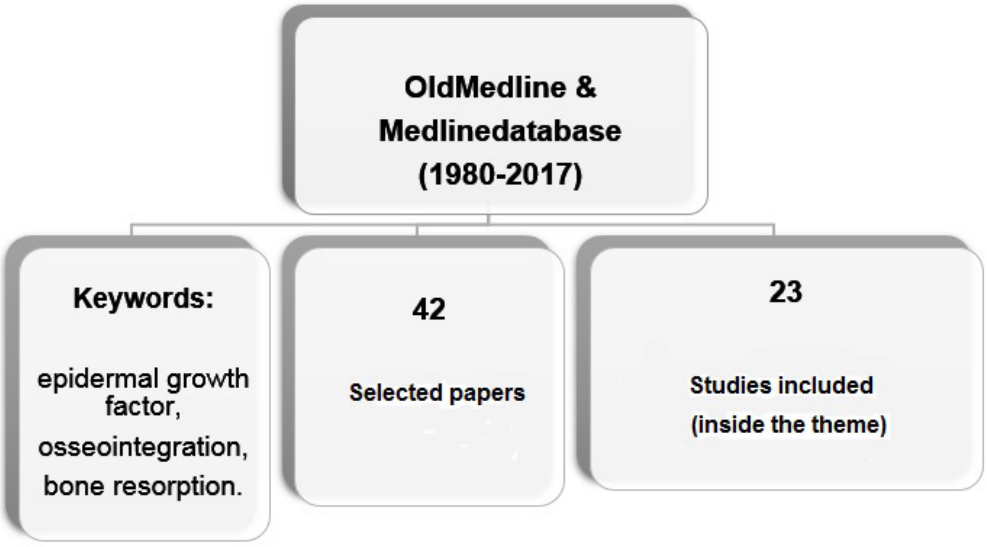

Figure 1. Medline Database Organogram

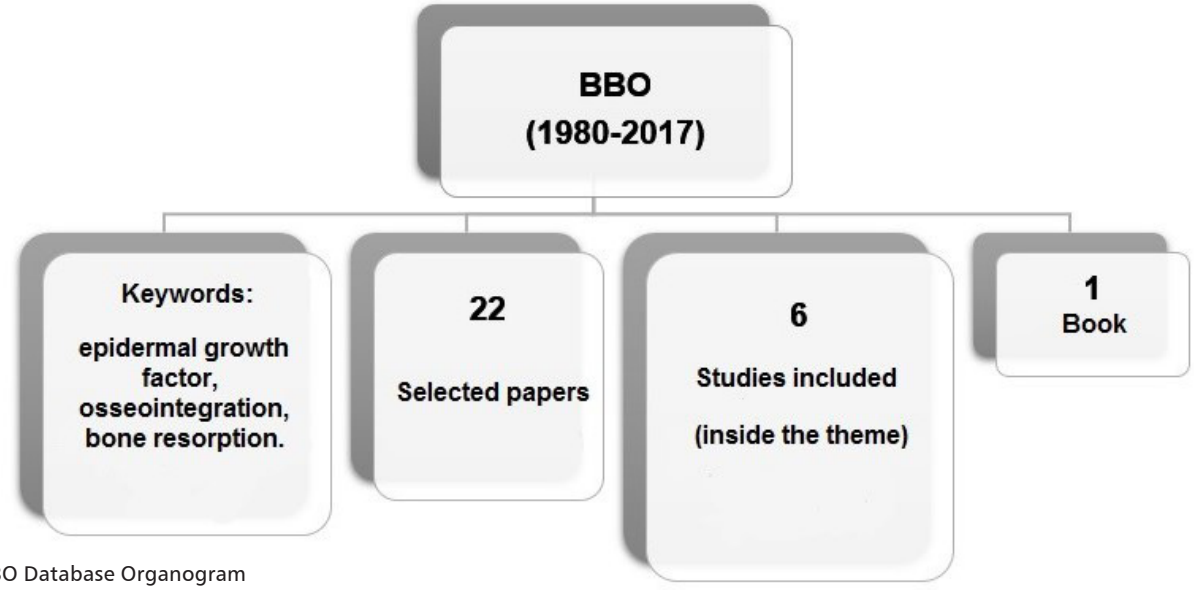

Figure 2. BBO Database Organogram

Literature Review

Winner of the Nobel Prize in Physiology and Medicine[8] (1986), Stanley Cohen (born 1922) isolated the Neural Growth Factor and the Epidermal Growth Factor.[1] In 1962,[3] the role of EGF in dental eruption and regulation of development.[9,10] Cohen described EGF in the submandibular glands of rats, elucidating their role in eruption of the incisors and palpebral opening of newborns.[3] EGF was patented in 1989 by Greg Brown for cosmetic purposes. gastric and buccal tissues.[11,12] In saliva, it fights gastric ulcers, since it stimulates the synthesis of DNA, protecting the mucosa against gastric acids, bile acids, pepsin, trypsin and bacteria.[13] In regeneration and repair , EGF is commonly associated with blood platelets produced by megakaryocytes in the bone marrow.[14,15] It is related to saucerization in bone integrated implants; and with the Malassez Epithelial Remains, preventing ankylosis, because it is responsible for the cellular resorption of the alveolar cortical bone.[16,17] In Ancient Greece, opium saliva was used to accelerate the healing of wounds in battle. Despite empiricism; it is possible to explain these apparently contradictory events by the action of EGF.[18] EGF excreted in saliva promotes proliferation, differentiation, keratinization and organization of the epithelium, mainly in regeneration and repair, particularly in cutaneous and mucosal ulcerations, after periodontal surgeries or removal of impacted third molars.[19,20] Malassez epithelial remains are cords or islets of epithelial cells, persistent in the periodontal ligament. In fact, fragments of 6 cells wide by 18 in length, whose origin dates back to apoptosis (programmed cell death) of the Hertwig Epithelial Sheath. These defects of malassez release prostaglandins and EGF, through an autocrine effect (mediators to act in neighboring cells), inducing, in the periodontal ligament, reabsorption of the bone crest, not exerting the same mechanism in the dental root. This is because the cementoblasts, which line the root, do not have receptors for EGF. Thus, the space of the 250 μm periodontal ligament tends to be preserved.[21] The first to describe the Malassez Epithelial Remains was Antoine Étienne Reynaud Augustin Serres (1786-1868). He believed it to belong to the periodontal ligament of newly erupted elements, suffering degeneration after post-eruptive maturation in adult life. The term Epithelial Remains of Serres or Glands of Serres was used as early as 1874, and it was believed that such islets had glandular or secretory functions.[1] However, Louis-Charles Malassez (1842-1909) won the claims of Epithelial Remains, in his publication dated 1885, although Serres described them in 1817. Such success comes from Malassez's discovery that epithelial cords persist in adulthood.[1] Hence Lartschneider's 1929 proposition, which differentiates between epithelial remnants from the gingiva, from those present in the periodontal ligament, and the latter should truly be called: Epithelial Remains of Malassez.[22]

Discussion

There is a premise that the morse cone connections induce a lower bone resorption when compared to resorptions due to external and internal hexagon connections. Generally implants, between the prosthetic part and fixation, have a gap, which facilitates bacterial colonization, inducing peri-implant inflammatory reactions. This junction between the prosthetic abutment and the implant is equally valid for cement-enamel junction in the natural tooth. One can thus consider that around the osseointegrated implant there is a biological space correspondent to the peri-implant groove, junctional epithelium and conjunctive insertion. Albrektsson *et al.*,[7] in 1986, demonstrated that 1.5 mm of bone loss around fixations in the first postoperative year was a success criterion for the external hexagon connections common to the time. Saucerization is thus considered to be much more a physiological event of maintenance of the integrality of biological distances, constituting a remodeling and not a pathological or pernicious event of responsibility of the type of connection employed.[23,24]

The peri-implant junctional epithelium has its beginning soon after the placement of the heeling or the intermediate or abutment, forming connections of the type hemidesmosomes and contact with the basal lamina. Removal of the intermediate would cause discrete inflammatory supepithelial infiltrates, hyperplasizing the epithelial cells; which will approach the alveolar bone crest, leading to more EGF, thus causing a resorptive increase. However, exposure of the peri-implant epithelium also exposes its cells to salivary EGFs, which have the function of maturing the epithelial lining, making it resistant. Although contradictory, Welander *et al.*,[25] in 2008, proved that constant removal of scarring and intermediates causes increased reabsorption at the level of the bone crest, making it more apical.

Contrarily, the placement of fixings with its cover; and, burial, does not promote the saucerization in the months before its reopening. Cervical resorption will only be seen when placing the prosthesis, the scar or the intermediate. It was believed that this came from the masticatory charges that caused resulting off the long axis implant, from bacterial contamination alone, or even from the deflection of bone tissue, rather as a compound of organic matter. Today, it is known that the beginning of the saucerization comes from the approximation of the epithelial tissue of the level of the alveolar bone crest. The connective tissue interposed between epithelium and bone crest neutralizes or minimizes the diffusion of the EGF, establishing over time a resorptive stabilization, which corresponds to the rounding of the right angle at implant placement, the maintenance of the space for the junctional epithelium and the conjunctive insertion, as well as the saucerization that occurs more slowly in subsequent years, around 0.1 mm / year, differently from

the first year, which is approximately 1 mm.[1,16,17,24]

Microbial biofilms release toxic products, lipopolysaccharides or endotoxins from anaerobic or Gram-negative bacteria, which promote intense release of mediators of inflammation. Being more tolerant to lipopolysaccharides, epithelial cells lining up sites of inflammation such as periodontal pockets, lesions promoted by periodontitis and peri-implantites. Epithelial cells have the innate function of separating the inner medium from the external buccal environment. Also, epithelial cells end up lining cavities without much selectivity, even tolerating regions or contaminated surfaces. This is not the case with specialized and differentiated cells such as fibroblasts, cementoblasts and conjunctive reinsertions. This may explain clearly the formation of a long junctional epithelium after scaling and coronary and root planing procedures or reconstructive periodontal surgeries. Another problem, now understood, concerns the exposure of spins and implant threads whose irregular topography, of the surface treatment, accumulates more biofilm, more inflammation, more EGF; finally, increased bone loss around fixations.[1,26-30]

Shifts in intermediates as to form have contributed to a better control of the saucerization process. Abutments with parallel walls usually leave the implant head promoting extensive saucerizations in vertical and horizontal directions. Cup-shaped intermediaries with a more compact implant immersion and a wider occlusal platform are preferable not to prevent vertical saucerization, however, to promote a lesser horizontal saucerization.[16,17] This understanding was fundamental to changes in the paradigm of manufacturers as well as well as new research initiatives on the behavior of the topography of the cervical region of the implant. The concave and non-parallel walls of the intermediates allowed sufficient space for apposition of junctional epithelium, conjunctive insertion and necessary separation between epithelium and bone crest, allowing a peri-implant biological space, as well as a controlled saucerization. What minimizes sauciation is the use of a prosthetic abutment with reduced diameter, which has nothing to do with the implant platform, whose dimensions remain constant. Recalling that the saucerization occurs in all osseointegrated implants, being neither dependent on its design, nor the surface topographic type, the platform used, nor the connection, much less the trademark; and neither of the profile of the patient submitted to treatment.[17,20,29,30]

Thus, it may be assumed that the saucerization may be primary: related to the first year of attachment fixation, during the formation of the peri-implant junctional epithelium (the formation phase of the "artificial" biological distances), in which the action of the EGFs is more present. Added to the secondary: after the first year of placement of the implant, in which biomechanical and biological factors would be acting. These include: surgical trauma, head and neck polishing of the implant, biological profile of the prosthetic abutment, supra-crestal tensions, contamination of the interface between the prosthetic abutment and the implant, over configuration caused by the prosthetic abutment, among others.[1,6,7,16,17,26,28,30]

Conclusion

The approximation of the epithelial tissue with the underlying cervical bone after implant placement with surgery facilitates EGFs to preponderantly act on cervical bone resorption in an attempt to maintain peri-implant biological distances. The successive changes in the design of commercial implants have contributed to a substantial evolution in Implantology.

References

1. Consolaro A. Reconstrução cervical peri-implantar: regeneração epithelial, EGF e a saucerização óssea (Capítulo 19). In: Consolaro A. Inflamação e reparo. Maringá: Dental Press; 2015; p.403-31.
2. Cohen S. Epidermal growth factor. Biosci Rep.1986;6(12):1017-28.
3. Cohen S. Isolation of a mouse submaxillary gland protein accelerating incisor eruption and eyelid opening in the new-born animal. J Biol Chem.1962;237:1555-62.
4. Gargiulo AW, Wentz FM, Orban B. Dimensions and relations of the dentogingival junction in humans. J Periodontol.1961;32(3):261-7.
5. Hasegawa N, Kawaguchi H, Ogawa T, Uchida T, Kurihara H. Immunohistochemical characteristics of epithelial cell rests of Malassez during cementum repair. J Periodontal Res. 2003;38(1):51-6.
6. Albrektsson T, Brånemark P-I, Hansson HA, Lindström J. Osseointegrated titanium implants: requeriments for ensuring a long-lasting, direct bone to implant anchorage in man. Acta Othop Scand.1981;52(2):155-70.
7. Albrektsson T, Zarb G, Worthington P, Eriksson AR. The long term efficacy of currently used dental implants: a review and proposed criteria of success. Int J Oral Maxillofac Implants.1986;1(1):11-25.
8.The Nobel Prize for Physiology or Medicine 1986 [editorial]. Science.1986;31;234:543-4.
9. Partanen AM, Thesleff I. Growth factor and tooth development. Int J Dev Biol. 1989;33(1):165-72.
10. Partanen AM, Thesleff I. Localization and quantitation of I125-epidermal growth factor brinding in mouse embryonic tooth and other embryonic tissues at different developmental stages. Dev Biol.1987;120(1):186-97.
11. Brown GL, Nanney LB, Griffen J, Cramer AB, Yancey JM, Curtsinger LJ, et al. Enhancement of wound healing by topical treatment with epidermal growth factor. N Engl J Med.1989;321(2):76-9.
12. Eckley CA, Costa HO. Estudo da concentração salivar do fator de crescimento epidérmico em indivíduos com laringite crônica por reflexo laringofaríngeo. Rev Bras Otorrinolaringol. 2003;69(5):590-7.
13. Venturi S, Venturi M. Iodine in evolution of salivary glands and in oral health. Nutr Health. 2009;20(2):119-34.
14. Ben-Ezra J, Sheibani K, Hwang DL, Lev-Ran A. Megakaryocyte synthesis is the source of epidermal growth factor in human platelets. Am J Pathol. 1990;137(4):755-9.
15. Mattila AL, Viinikka L, Saario I, Perheentupa J. Human epidermal growth renal production and absence from plasma. Regul Pept.1988;23(1):89-93.
16. Consolaro A, Carvalho RS, Francischone Jr CE, Francischone CE. Mecanismo de saucerização nos implantes osseointegrados. Rev Dental Press Periodontia Implantol. 2010;4(1):37-54.
17. Consolaro A, Consolaro MFMO. As funções dos Restos Epiteliais de Malas-

sez, o EGF e o movimento ortodôntico ou Por que o movimento ortodôntico não promove a anquilose alveolodentária? Dental Press J Orthod. 2010;15(2):24-32.
18. Angeletti LR, Agrimi U, Curia C, French D, Mariani-Costantini R. Healing rituals and sacred serpents. Lancet.1992;340(8813):223-325.
19. Ohshima M, Sato M, Ishikawa M, Maeno M, Otsuka K. Physiologic levels of epidermal growth factor in saliva stimulate cell migration of an oral epithelial cell line.HO-1-N-1. Eur J Oral Sci. 2002;110(2):130-6.
20. Pesonen K, Vinikka L, Koshimies A, Banks AR, Nicolson M, Perheentupa J. Size heterogeneity of epidermal growth factor in human body fluids. Life Sci. 1987;40(26):2489-94.
21. Wallace JA, Vergona K. Epithelial rest´s function in replantation: is splinting necessary in replantation? Oral Surg Oral Med Oral Pathol.1990;70(5):644-9.
22. Thesleff I. Epithelian cells rests of Malassez bind epidermal growth factor intensely. J Periodont Res.1987;22(5):577-80.
23. Perrotti V, Lorenzo R, Ricci L, Doi K, Piattelli A, Shibli JA, et al. Radiographic comparison of periimplant bone resorption and assessment of survival rates of 2 implant systems. Implant Dent. 2015;24:77-82.
24. Pola JD, Pimentel AC, Brandt WC, Roman-Torres CVG, Boaro LC, Sendyk WR. Avaliação da microinfiltração entre o implante dentário e pilar protético em função dos diferentes tiposde conexãoe métodos de vedação. J Biodent Biomat. 2016;6:28-55.
25. Welander M, Abrahamsson I, Berglundh T. The mucosal barrier at implant abutments of different materials. Clin Oral Implants Res. 2008;19(7):635-41.
26. Lima JHC, Tanaka MN, Bezerra FJB, Maia VTG, Robbs PCM. Avaliação functional de implantes por mineralização óssea in vitro. Rev Bras Odontol. 2015;72(1/2):92-5.
27. Neri JFA, Tunes RS, Barreto Ma, Leal Jr MS, Oliveira CAB, Tunes UR. Doença Peri-implantar em paciente com diabetes mellitus tipo 2: relato de caso. Rev Bahiana Odontol. 2016;7(4):262-71.
28. Romanos GE, Javed F, Delgado-Ruiz RA, Calvo-Guirado JL. Peri-implant diseases: a review of treatment interventions. Dent Clin N Am. 2015;59:157-78.
29. Baltacioğlu E, Korkmaz FM, Bağiş N, Aydın G, Yuva P, Korkmaz YT, et al. Combined soft and hard tissue peri-implant plastic surgery techniques o enhance implant rehabilitation: a case report. Open Dent J. 2014;28(8):207-12.
30. Mangano C, Shibli JA, Pires JT, Luongo G, Piattelli A, Lezzi G. Early Bone Formation around Immediately Loaded Transitional Implants Inserted in the Human Posterior Maxilla: The Effects of Fixture Design and Surface. Biomed Res Int. 2017;2017:4152506.

Mini Curriculum and Author's Contribution

1. Luciano Bonatelli Bispo – DDS and PhD. Contribution: Study desing, article research and writing, final approval.
2. Caleb Shitsuka – DDS and PhD. Contribution: Article research and writing, final approval

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