EXPERT VIEW/REVIEW PAPER

The Vital Role of Nitric Oxide in the Healing of Dental Implant Patients

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Abstract

Background: Nitric oxide, a diatomic free radical activated by phagocytic leukocytes, arginine a catalyzed product that is synthesized by nitric oxide synthases. It is one of the mechanisms which assists in the resolution of inflammation. A review of its effect on healing around dental implants is yet to be studied.

Objective: To review the role of nitric oxide on healing around dental implants.

Material and methods: A digital search was carried out using Google Scholar, Medline, and PubMed. The most related article was selected for the review.

Conclusion: Osseointegration of dental implants is inclined by many factors which affect the bone-implant contact formation process, and it initiates by forming a hematoma, immunomodulation, and angiogenesis following osteogenesis. Nitric oxide shows a biphasic effect on osteoblast and osteoclast activity, which depends on the concentration of nitric oxide and it can be an important factor in achieving successful osseointegration.

Keywords: Dental implants, Healing, Nitric oxide, Osseointegration.

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Introduction

Dental implant therapy involves a process where osteotomy is done, followed by implant placement and tissue suturing. One of the major processes prior to wound healing is the process of inflammation which is a fundamental element of the immune host response to infection-causing agents and tissue damage. Numerous inflammatory changes do take place at the cellular level, including the release of proinflammatory cytokines notably IL-6, and TNF-α.[1] There are several self-regulating methods for reestablishing homeostasis, and one of the crucial biological processes is the potential of endothelial nitric oxide synthase to derive nitric oxide (NO) from the vascular endothelium through the L-arginine-NOS pathway. As a diatomic free radical, nitric oxide is abundantly created by phagocytic leukocytes that have been activated. It is a catalyzed product of arginine which is synthesized by nitric oxide synthases (NOS) (Fig. 1).[2]

Nitric oxide has a substantial role in regulating the blood flow for vascular integrity maintenance. Dietary nitrate can produce nitric oxide via the enterosalivary nitrate-nitrite-NO pathway, which has demonstrated its therapeutic and preventative potential, in addition to endogenous nitric oxide generation via the L-arginine-NOS pathway. In the enterosalivary nitrate-nitrite-NO route, dietary nitrate is absorbed into the bloodstream, followed by absorption by the salivary glands, and then reduction to nitrite by commensal bacteria in the mouth.

Metalloproteins (such as hemoglobin and deoxyhemoglobin), enzymes (such as xanthine oxidoreductase), and other substances with redox potential convert nitrite present in swallowed saliva to nitric oxide (e.g., polyphenols). In low oxygen or acidic environments, nitrite reduction to nitric oxide accelerates, which is advantageous during tissue ischemia.[3] This narrative review will provide information on how nitric oxide affects the healing around dental implants.

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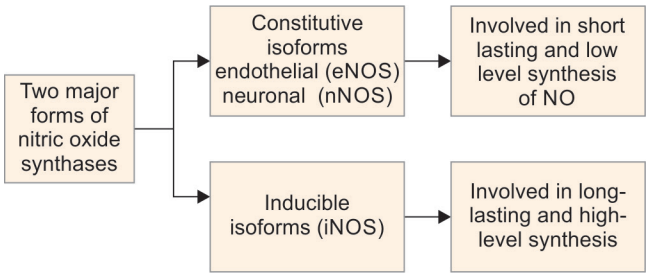

Fig. 1: Forms of nitric oxide synthases

Influence of Nitric Oxide on Bone Mass Regulation and Metabolism

Implantation of any biomaterial can instantly activate the innate immune system which leads to the development of an acute inflammatory state that marks the initial step of tissue repair. Macrophages, being an important factor in the immune response, their population has main two phenotypes: proinflammatory (M1) and anti-inflammatory (M2). For the promotion of differentiation

of mesenchymal stem cells into osteoblasts and osteocytes, many cytokines are secreted by the inflammatory macrophages during the acute inflammatory phase. This acute inflammatory state aids in bone remodeling, but chronic inflammation may develop if it persists for a long time, and it may also boost the activity of osteoclasts, which regulate the entire osseointegration process. Apart from this, the inflammatory cytokines also have an inducive effect on the secretion of other growth factors like VEGF which assists in the healing process, post-dental implant placement. After implantation, from the third day, the inflammatory response begins to reduce. Thus, for creating an ideal microenvironment surrounding dental implants to ensure osseointegration, a change from the inflammatory phase to the regenerative phase is needed.[4] Numerous biological, functional, and inflammatory processes, such as vasodilation, modulation of neurotransmission, and inhibition of microbial and tumor cell growth, have demonstrated the importance of nitric oxide in them. The three nitric oxide synthase (NOS) isoforms, which are active in various cell types and are released with different kinetics, are responsible for the various effects of nitric oxide. Since bone is a multicellular complex structure, it constantly undergoes "bone remodeling," a process of renewal and repair. In response to the expression of lineage-specific regulatory molecules such as c-fos, RANK ligand (RANKL), M-CSF RANK (receptor activator of NFkB), and osteoprotegerin, osteoclasts—multinucleated cells of hemopoietic origin—differentiate from monocyte/macrophage lineage progenitors (OPG). When the transcription factor Cbfa1 is activated, mesenchymal cells in the bone marrow called stromal cells undergo a differentiation process into osteoblasts.[5]

Nitric oxide shows a biphasic effect on the bone remodeling process, as it is produced by osteoblasts constitutively, which acts as a stimulator for the growth of osteoblasts and also in the secretion of cytokines. Because low levels of nitric oxide affect the release of IL-1, which primarily affects osteoblasts by enhancing nitric oxide synthesis through the iNOS pathway and promotes nuclear translocation of the transcription factor NFkB in osteoclast progenitors, low levels of nitric oxide may result in bone resorption. However, NFkB activation in response to IL-1 is also briefly seen in osteoclast progenitors from iNOS-deficient people, proving that nitric oxide plays a role in encouraging NFkB activation in osteoclast precursors. Because of the inhibition of osteoclast formation, activity, and nitric oxide-induced death of osteoclast progenitors, high concentrations of nitric oxide have a suppressive impact.[6]

In directed bone regeneration therapy situations, the periosteal cells can develop into osteoblasts by constantly producing mature osteoblasts from periosteal progenitor cells, leading to radial bone production during fracture repair. Osteocytes are osteoblasts that have undergone lethal differentiation and help build the connective dendritic processes and mineralize bone. Osteocytes are known to be the key elements in the regulation of bone homeostasis because of their ability to release signaling factors to employee osteoclasts at the osseointegration site. Thus, successful implant osseointegration necessitates a sustained presence and relocation of differentiated osteogenic cells at the implantation site during the osteogenesis for de novo bone formation.[7]

Effect of Nitric Oxide on Healing of Dental Implants

Maximal bone-implant contact after osseointegration determines successful rehabilitation after dental implant placement, where osteoinductive and osteoconductive processes play a significant role. Periosteum and osteocytic activity at the cellular level predict bone homeostasis.[8] Tözüm et al.[9] analyzed the probable influence of clinical status, inflammation severity, and prosthesis loading effect on nitric oxide concentration around dental implants. Results showed an increase in nitric oxide concentration with the presence of inflammation and its severity which shows its role in the peri-implant inflammatory process. Tözüm et al.[10] quantified peri-implant sulcular fluid nitrite levels as part of a longitudinal study to evaluate potential changes in nitric oxide concentration in relation to the clinical condition of the peri-implant site based on the loading pattern of dental implants.[11] Nitric Oxide concentration, as reflected by PISF nitrite levels, demonstrated differences between early loaded and delayed loaded implants.[12,13] Due to changes in the magnitude of stresses and how they were transmitted to the supporting bone, the nitric oxide concentration around the dental implant was affected. Additional factors included the anatomical positioning of the dental implant site, the quality of the bone, the implant technique used, the size of the implants, the design of the prosthesis, and variations. Tözüm et al.[11] also demonstrated that loading of implants has its effect on nitric oxide concentration and thus, it can be ventured that peri implant sulcular fluid volume can be an indicator of implant stability, and nitric oxide concentration can predict peri-implant soft tissue inflammation. Apart from bone remodeling, nitric oxide enhances the migration and proliferation of fibroblasts and ensures connective tissue formation.[14] In physiological conditions, nitric oxide released from the endothelium helps in regulating vascular tonicity and preserves vascular integrity by averting platelet accumulation and decreasing the expression of adhesion molecules. Nitric oxide, one of the second messengers involved in wound healing, can function as an autocrine or paracrine messenger in general host defense. Nitric oxide generation is increased dose-dependently as a result of laser stimulation, which further encourages cell division and re-epithelialization.[15]

According to Loi et al.,[16] 72 hours of an inflammatory state is required to predict normal osteogenesis, and starting on the third post-implantation day, osteoclastic influence must diminish to confirm that osteogenic differentiation is being positively regulated. Chen et al.[17] concluded in their study that unjustified activation of proinflammatory macrophages would lead to the release of proinflammatory cytokines, mediating MMP secretion and osteoclast differentiation, adversely affecting wound healing and bone remodeling. Zhao et al.[18] reported that nitric oxide is a domineering signaling molecule in bone remodeling activity by activating cAMP/PKA, and MAPK pathways. It decreases as the inflammatory cytokine signals are eradicated. Zhang et al.[19] confirmed that the synergism of L-arginine supplement, plasmids transfection, and calcium ions can be a hopeful therapeutic approach.[20]

Conclusion

Dental implants have become one of the most preferred choices of treatment in the current era of advanced technology which predicts accuracy right from placement of implants to the prosthesis. But one factor which technology cannot manage is the Host factor. Each and every individual is different depending on their age, medical complication, gender, etc. Osseointegration of dental implants is determined by numerous factors starting from inflammation, and host response to the bone remodeling process. The effect of nitric oxide on the healing of dental implants is one of the lesser-explored aspects. Nitric oxide plays a significant role in bone remodeling by predicting the osteoblastic and osteoclastic activity, and induces a positive effect on other growth factors involved in the healing

process, which is governed by its concentration. Further, nitric oxide provides a helping hand in collagen formation, connective tissue formation which supports achieving an excellent esthetic soft tissue profile for the final prosthetic rehabilitation. Nitric oxide concentration around dental implants acts as an indicator to predict the presence of peri-implant inflammation, which can be affected by the loading protocols. Evidence have shown the effect of nitric oxide concentration on the sign and symptoms of inflammation and its further progression. Thus, it can be concluded that nitric oxide plays a vital role at every step of healing around dental implants.

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