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Review Article

Role of the NF- κ B Signaling Pathway in Oral Surgery: Regulation of Inflammation, Bone Remodeling and Implant Success

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Abstract

Controlled inflammatory responses play a crucial role in soft tissue healing, bone remodeling and the osseointegration of dental implants in oral surgery. There is an intricate relationship between the signaling pathway of Nuclear Factor-kappa B (NF- κ B), which regulates immune responses and cellular fate and what we know of immunology, bone biology and implantology. This review aims to connect the molecular mechanisms of NF- κ B regulation in order to provide an integrated immuno-biological perspective on modern surgery. For the purpose of conducting a thorough literature search, the information was retrieved from PubMed, Scopus and Web of Science databases for peer-reviewed articles which appeared up to 2026. The key words for research were: Canonical and non-canonical NF- κ B pathways, alveolar bone turnover, polarization of macrophages, immunomodulating biomaterials and peri-implant diseases. The findings illustrate that the activation of the canonical NF- κ B pathway, which happens immediately after surgery, is of utmost importance for the recruitment of immune cells, debris elimination and early angiogenesis. The inflammatory process continues and then declines, allowing M2 macrophage polarization and osteoblast differentiation to take place. In this case, the undesired constant regulation of NF- κ B, caused by presence of bacterial biofilms, injuries received during surgery as a result of too intrusive operations and systemic risk factors, leads to chronic inflammation, RANKL-induced activation of osteoclasts and consequently, to the bone loss near the implants. Clinical success is achieved through the use of effective timing of NF- κ B signaling outcomes instead of complete blocking of signaling pathways. Different methods are used for the delivery of information in order to transform the inflammatory response into stimulation processes associated with the generation of bone tissue and longevity of the implants.

Key words: NF- κ B signaling, oral surgery, dental implants, osseointegration, alveolar bone remodeling, macrophage polarization, immunomodulatory biomaterials

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INTRODUCTION

The successful performance of surgical implantology depends on the right regulation of inflammation, wound healing and bone remodeling, which determine tissue regeneration, preservation of the alveolar bone and stability of the implant in the long-term. The exact start and timely ending of these biological processes are important for predictable healing. Their malfunction can result in delayed repair, excessive bone loss and unsuccessful osseointegration. The surgical environment within the oral cavity is particularly challenging due to the large number of microorganisms within the mouth, ongoing stresses to the surrounding soft and hard tissues caused by chewing, the rapid rate at which the human body heals and the proximity of bone and soft tissues¹⁻⁴. For an oral surgeon to have a successful outcome, there must be a finely regulated inflammatory response that occurs and subsequently leads to repair of the surgically treated area⁵. The NF- κ B system is central to the biological transitions occurring after oral surgery, as it converts information received from surgical trauma, bacteria, or foreign bodies into a genomic program concerning the development of the immune system's cells, production of cytokines and differentiation of bone cells into their respective roles⁶⁻⁸.

The healing of the extraction socket, stability of periodontal and peri-implant tissues, preservation of the alveolar ridge and long-term survival of dental implants are influenced by the activity of NF- κ B in oral and maxillofacial surgery⁹. Acute NF- κ B activation is critical for starting the wound healing process; however, chronic signaling induces pathological bone loss, fibrous encapsulation and failure of implants^{6,8,9}. By understanding the kinetics of NF- κ B signaling, cellular targets for its actions and how to modulate its activity, oral surgeons will be positioned to improve their operative technique, use immune-compatible biomaterials and provide adjunctive therapies while taking advantage of the natural biology of oral tissue regeneration^{7,8}. Although important progress has been achieved in the understanding of NF- κ B biology, there is grand fragmentation of current knowledge of this issue among immunology, bone biology and implant research without adequate integration into oral surgery field. In addition, the latest findings about immunomodulatory materials, macrophage polarization, intracellular signaling and targeted therapy have not been properly integrated into the knowledge about clinical application in oral wound healing and implant integration process. Hence, the need for a recent review that will bridge

different aspects of molecular processes with contemporary practice in oral surgery and newly-born approaches in regenerative dentistry.

This review integrates current information regarding NF- κ B modulation, creating a platform for establishing its role as a foundation of contemporary oral surgical practice. Given its role in controlling inflammation, bone remodeling and tissue repair, we consider NF- κ B an appropriate target for achieving greater results in oral surgery. Studying this pathway may help develop targeted medical approaches that use minimally invasive surgery, immunosuppressive products and localized therapies for achieving better healing. The present study summarizes the information about NF- κ B, its function in oral surgery and ways to optimize healing processes.

MATERIALS AND METHODS

A narrative literature review was designed to gather evidence about the influence of Nuclear Factor Kappa B signaling on oral surgery, emphasizing inflammation and healing, the processes of forming alveolar bone, macrophage polarization, osseointegration and peri-implant diseases and the use of therapeutic immunomodulation. The sources of information were obtained via databases such as PubMed, Scopus and Web of Science.

The authors used keywords such as "NF- κ B signaling", "canonical NF- κ B pathway", "non-canonical NF- κ B pathway", "oral surgery", "oral wound healing", "alveolar bone remodeling", "bone turnover", "macrophage polarization", "dental implants", "osseointegration", "peri-implantitis", "peri-implant disease", "immunomodulatory biomaterials" and "NF- κ B modulation" when conducting the research. Boolean operators (AND/OR) were used in terms of combining the core concepts. The databases were searched for relevant peer-reviewed publications available up to 2026.

When qualifying the papers, the researchers searched for peer-reviewed research materials that contained relevant information about NF- κ B signaling processes or its role in clinical applications in the sphere of oral and maxillofacial surgery, processes associated with changing the bone structure, wound healing, osseointegration of dental implants, peri-implant diseases including inflammation and the use of immunomodulation-related methods. Original research and literature reviews were both regarded as acceptable for this purpose. The authors disregarded papers that were connected to NF- κ B signalling or oral and maxillofacial surgery, but did not contain enough information and were not relevant to the goals of the given project.

MOLECULAR ARCHITECTURE OF NF- κ B IN THE ORAL CAVITY

Nuclear factor-kappa B (NF- κ B) signaling pathways consist of two interdependent cascades, the canonical (classical) and non-canonical (alternative) pathways^{7,10,11}. In healthy oral fibroblasts, osteoblasts and resident immune cells at rest, NF- κ B dimers are sequestered in the cytoplasm by inhibitory I κ B proteins^{6,12}. Following surgical trauma or exposure to bacterial lipopolysaccharides or pro-inflammatory cytokines, the canonical pathway is rapidly activated⁸. The IKK complex in the canonical pathway leads to the phosphorylation of I κ B via the proteasome and subsequent translocation of released p65/p50 dimers from the cytoplasm to the nucleus, where they stimulate transcription of genes involved in the establishment of acute inflammation, antimicrobial defense and cell survival¹³.

The non-canonical pathway of NF- κ B signal transduction responds only to a limited subset of stimuli (e.g., BAFF and CD40 ligands) and requires NIK-mediated processing of p100 to p52 as its principal mechanism of transduction¹⁰. The RelB/p52 heterodimer transcriptionally regulates the organization of lymphoid tissues, B-cell maturation and adaptive changes associated with chronic immunity¹⁰. In the oral cavity, these pathways are not isolated from but rather interact extensively with Wnt, MAPK and metabolic signaling pathways to direct either regeneration or chronic pathology at a surgical site^{8,14}. Post-translational modification events, chromatin accessibility variations and non-coding RNA networks all further fine-tune NF- κ B output across distinct populations of oral cells, demonstrating the necessity for microenvironment-specific therapeutic strategies¹⁵.

Crucially, this molecular architecture serves as the direct biological link determining how intracellular cascade triggers manifest as visible macro-tissue alterations during alveolar ridge healing and bone remodeling.

NF- κ B IN ORAL WOUND HEALING AND ALVEOLAR BONE TURNOVER

There is a consistent progression of the alveolar bone's remodeling process and invasion of the replaced socket, beginning with hemostasis (the prevention of blood loss), followed by inflammatory reactions, the proliferation of new blood supply and cells and finally maturation of the bone^{4,5,9}. In the early stages after tooth extraction or periodontal surgery, NF- κ B (nuclear factor-kappa B) activation peaks between 48 and 72 hrs, regulating neutrophil infiltration,

macrophage recruitment and the production of IL-1, TNF- α and IL-6⁶⁻⁸. This early wave of inflammation clears dead tissue from the socket, stimulates the development of blood vessels (angiogenesis) and creates a scaffold that promotes subsequent bone deposition^{4,7,9}.

In the proliferative phase, the signaling through NF- κ B gradually decreases as the macrophages shift from the inflammatory (M1) phenotype to the pro-growth (M2) phenotype^{4,8}. The M2 macrophages produce Wnt ligands, TGF- β and IL-10, all of which inhibit excessive NF- κ B activity and promote bone cell maturation^{7,8,14}. The limited expression of RANKL in the socket promotes a limited osteoclastic activity to remodel the initial matrix of bone in the socket^{6,9}. If the NF- κ B pathway remains dysregulated and results in high levels of NF- κ B due to a persistent M1-dominated site, excessive operative trauma, granulation tissue remaining in the socket, or the presence of microorganisms, delayed healing of the socket, rapid resorption of bone from the alveolar ridge, or delayed integration of graft materials will characterize the sockets^{1,2,4,6,9}.

This precise balance of cellular turnover sets the biological foundation for how raw bone tissue interacts with foreign implant biomaterials during the complex phases of osseointegration.

NF- κ B DYNAMICS IN DENTAL IMPLANT OSSEOINTEGRATION

Successful dental implants require a direct functional and structural relationship with the implant surface and with the surrounding living bone. Osseointegration is an immune-mediated process regulated by NF- κ B activity^{6,8,9}. Based on the dynamics of this signaling, this process can be conceptualized into three phases of NF- κ B kinetics (Table 1):

- **Early phase (Days 0-7):** Following implant insertion, microtrauma occurs and the surrounding damaged tissue releases damage-associated molecular patterns (DAMPs) into the environment¹⁶. This results in the activation of transient NF- κ B (Nuclear Factor- κ B), which recruits macrophages and starts to initiate the cytokine signaling pathway that is necessary for both vascular ingrowth and for the early homing of mesenchymal stem cells (MSCs)^{4,6,8}. If inflammation is controlled during this phase, it is a protective factor against inadequate healing^{4,9}. Adjunctive therapies like Low-Level Laser Treatment (LLLT) have demonstrated a clinical capacity to positively regulate early hard and soft tissue healing around implants during this sensitive therapeutic window¹⁷

Table 1: Functional roles and temporal dynamics of NF- κ B signaling during oral wound healing and dental implant osseointegration

Healing phase	NF- κ B activity	Key cellular events	Biological outcome	Clinical relevance	Key references
Early inflammatory phase (0-7 days)	Transient activation via canonical pathway	Neutrophil infiltration, macrophage recruitment, release of IL-1, TNF- α and IL-6, angiogenesis initiation	Debridement of damaged tissue and establishment of healing microenvironment	Essential for extraction socket healing and early implant integration	Zhao <i>et al.</i> ⁴ , Chen <i>et al.</i> ⁶ , Huang <i>et al.</i> ⁹ , Kaushal <i>et al.</i> ¹⁶ , Chen <i>et al.</i> ¹⁷
Intermediate remodeling phase (1-4 weeks)	Gradual decline of activity	Transition from M1 to M2 macrophages, controlled osteoclastogenesis via RANKL, initiation of osteogenesis	Coupled bone resorption and new bone formation	Supports stable osseointegration and graft incorporation	Chen <i>et al.</i> ⁶ , Guo <i>et al.</i> ⁸ , Boyce and Xing ¹⁸ , Shirazi <i>et al.</i> ²¹ , Newman <i>et al.</i> ²³ , Hotchkiss <i>et al.</i> ²⁴
Late regenerative phase (4-12 weeks and beyond)	Low physiological activity	Wnt/ β -catenin signalling predominates, osteoblast maturation, matrix mineralization	Mature bone formation and implant stability	Long-term implant success	Chang <i>et al.</i> ²⁰ , Shirazi <i>et al.</i> ²¹ , Newman <i>et al.</i> ²³ , Kafas <i>et al.</i> ²⁵
Persistent activation	Sustained NF- κ B signaling	M1 macrophage predominance, excessive RANKL expression, osteocyte apoptosis, impaired osteoblast differentiation dysregulated	Chronic inflammation, bone loss, fibrous encapsulation	Peri-implantitis, delayed healing, implant failure	Chen <i>et al.</i> ⁶ , Guo <i>et al.</i> ⁸ , Huan <i>et al.</i> ⁹ , Boyce and Xing ¹⁸ , Chang <i>et al.</i> ²⁰ , Newman <i>et al.</i> ²³ , Hotchkiss <i>et al.</i> ²⁴ , Alrabiah <i>et al.</i> ²⁶ , Insua <i>et al.</i> ²⁹

- **Intermediate phase (Weeks 1-4):** During this time, osteoclasts mediate remodeling of bone to prepare the implant site (i.e., implant bed) for osseointegration. NF- κ B is responsible for initiating osteoclast differentiation via RANKL (Receptor Activator of Nuclear Factor- κ B Ligand) and simultaneously downregulating osteoblast maturation¹⁸⁻²⁰. As such, the balanced transition from osteoclastic resorption to osteogenic deposition will ensure that the resorption is precisely followed by appropriate new bone deposition along the implant surface²¹. Additionally, the inclusion of local therapeutic modulators like melatonin has shown promise in enhancing bone formation and optimizing early osseointegration pathways²²
- **Late phase (Weeks 4-12 and beyond):** Once an adequate volume of bone is present at the implant site, NF- κ B activity should decrease and Wnt/ β -catenin (Wnt pathway) will dominate cellular signaling²⁰⁻²¹. Persistent activation of NF- κ B leads to inadequate healing and indicates that the previously mentioned physiological processes have been disrupted, resulting in infiltration of chronic macrophages, apoptosis of osteocytes and the development of fibrous interposition tissue²³

Furthermore, excessive implant torquing, micromotion at the implant/bone interface and/or non-ideal surface chemistry may prolong NF- κ B signaling, which could fail osseointegration and early implant mobility²³.

The surface properties of implants are important in determining how they will interact with macrophages and immune cell types^{14,21}. Roughness on the implant surface supports M2 polarization of macrophages, decreases the overstimulation of NF- κ B and contributes to the formation of bone-to-implant contact^{14,21,23}. Implant surface characteristics that do not exhibit optimal surface energy could modify macrophage activation and resolution of inflammation, resulting in increased risk of peri-implant bone resorption²⁴. To properly evaluate these dynamic shifts, modern clinical assessment tools must accurately track objective changes in implant stability indices over time to gauge true healing status²⁵.

When these biomechanical or biochemical thresholds are crossed, the homeostatic downregulation of NF- κ B fails, triggering localized tissue destruction and severe clinical pathologies.

CHRONIC INFLAMMATION, PERI-IMPLANT DISEASE AND ORAL PATHOLOGY

Chronic inflammatory disease development will occur more frequently within the oral cavity from an unregulated activation of NF- κ B and lack of regulation through physiologic means^{6,8}. An example is peri-implantitis, where there exist the circumstances of biofilm, defective host defenses and ongoing NF- κ B activation, resulting in a self-perpetuating cycle involving predominance of M1 macrophages, increased levels

of RANKL and subsequent bone loss of crestal bone^{18,23,24}. Similar mechanisms seen in peri-implantitis can be found in the clinical presentation of refractory chronic periodontitis in which activation of NF- κ B continues within both oral mucosal fibroblasts and osteoclast precursors, leading to loss of attachment and resulting in destruction of alveolar bone^{6,9,18}.

As previously described, systemic conditions experienced by oral surgery patients frequently interfere with the normal functioning of NF- κ B^{6,8}. For example, individuals with diabetes develop a build-up of advanced glycation end-products which cause chronic activation of the IKK pathway and maintain an NF- κ B associated state of inflammation. This chronic state of inflammation in turn leads to poor socket healing and poor graft consolidation^{4,6,8,26}. Smoking is also implicated in the development of oxidative stress and vasoconstriction resulting in macrophages around implants being polarized to a sustained M1 state for extended periods of time^{23,24}. Systemic metabolic disturbances such as hyperlipidemia may increase oxidative stress and thereby impair osteoblast function, favor bone resorption and compromise both bone regeneration and implant osseointegration²⁷. Emerging evidence indicates that statins may favor dental implant osseointegration by modulating molecular pathways, including NF- κ B inhibition, thereby potentially supporting bone formation and healing²⁸. Through altering rates of bone remodeling and interfering with the resolution of inflammation, bisphosphonate-related osteonecrosis of the jaw establishes a microenvironment in which NF- κ B signaling does not transition from active repair to homeostasis, leading individuals with osteonecrosis to have exposed necrotic bone and delayed epithelial closure^{4,6,23}.

SURGICAL AND BIOMATERIAL STRATEGIES FOR NF- κ B MODULATION

Utilizing immune modulation methods to improve the dynamics of NF- κ B is becoming more common in the field of modern oral surgical practice. Several strategies have exhibited clinical and experimental merit, including (Table 2):

- **Immunoresponsive biomaterials:** Surface modifications that encourage the change of macrophages from the M1 to M2 phenotype can limit the extent of NF- κ B signaling activation²¹. For example, hydrophilic titanium surfaces, calcium phosphate coatings, strontium-doped materials and magnesium-releasing membranes work to downregulate the activity of IKK while upregulating the Wnt and TGF-beta signaling pathways^{21,30}.
 - **Localized pharmacological modulation:** Complete inhibition of NF- κ B leads to a host's inability to fight infections and will delay the healing process^{8,23}. Other localized strategies aimed at promoting the resolution of inflammation and facilitating the transition from inflammatory to tissue-repairing signaling may be to use NF- κ B decoy oligodeoxynucleotides as decoys in the local environment to sequester active dimers⁹. Novel biochemical interventions, such as topical melatonin administration, can serve as localized modulators that minimize destructive inflammatory pathways while accelerating bone deposition pathways around the implant fixture²². Delivery by means of hydrogel and biodegradable scaffold can achieve a local sustained site-specific drug delivery without causing an undesired systemic effect³⁰.
 - **Staged loading and biomechanical control:** The early or immediate load on an implant placed in bone that is non-integrated or compromised will have increased mechanical stress on the bone-implant interface, which is thought to prolong the inflammatory signaling and to therefore affect osseointegration and healing^{23,29}. This is likely to negatively affect osseointegration and delay healing. The following techniques can reduce stress and allow transition from inflammatory to regenerative state, prior to applying functional load such as late loading of the dental implant, applying proper occlusal guidance and use of splints^{23,29}.
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- **Minimally traumatic surgical protocols:** The use of specific osteotomy preparation techniques, controlled drill speeds, sufficient irrigation and preventing the application of excessive insertion torque can prevent osteocyte damage and thereby limit the release of DAMPs into the area, thus preventing unnecessary activation of NF- κ B through an aberrant mechanism²⁹. In addition, subcrestal placement and the technique of platform switching help to distribute the mechanical stress evenly, promoting preservation of peri-implant bone homeostasis²⁹.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS IN ORAL SURGERY

The incorporation of NF- κ B biology into oral surgery represents a significant departure from the traditional mechanical approach to treatment through a new paradigm of immuno-biologically based treatment planning^{8,14,21,23}. The clinician must be aware that inflammation has no inherently negative aspects; only the duration, intensity and composition influence the ultimate clinical outcome^{8,23}. Preoperative risk assessments should consider the systemic inflammatory burden, level of glycemic control, smoking history and periodontal history, all of which could affect the kinetics of NF- κ B^{6,8,23,24}.

Table 2: Therapeutic and surgical strategies for modulating NF- κ B signaling to promote healing and osseointegration in oral surgery

Strategy	Mechanism of action	Effect on NF- κ B signaling	Expected clinical benefit	Key references
Minimally traumatic surgical protocols	Reduced tissue injury and DAMP release	Limits excessive activation	Faster healing and improved implant stability	Zhao <i>et al.</i> ⁴ , Newman <i>et al.</i> ²³ , Insua <i>et al.</i> ²⁹
Hydrophilic titanium surfaces	Promotion of M2 macrophage phenotype	Facilitates resolution of inflammation	Enhanced osseointegration	Ma and Hottiger ¹⁴ , Shirazi <i>et al.</i> ²¹ , Newman <i>et al.</i> ²³ , Hotchkiss <i>et al.</i> ²⁴ , Li <i>et al.</i> ³⁰ , Mukaddam <i>et al.</i> ³⁵
Calcium phosphate coatings	Immunomodulation and osteogenic stimulation	Downregulates inflammatory signaling	Improved bone regeneration	Shirazi <i>et al.</i> ²¹ , Li <i>et al.</i> ³⁰ , Emam <i>et al.</i> ³⁴
Strontium-doped biomaterials	Osteogenic and anti-inflammatory effects	Suppresses excessive NF- κ B activity	Increased bone formation	Shirazi <i>et al.</i> ²¹ , Li <i>et al.</i> ³⁰ , Emam <i>et al.</i> ³⁴
Magnesium-releasing membranes	Modulation of macrophage behaviour	Supports transition to regenerative state	Improved GBR outcomes	Shirazi <i>et al.</i> ²¹ , Li <i>et al.</i> ³⁰
NF- κ B decoy oligodeoxynucleotides	Sequestration of active NF- κ B dimers	Localized inhibition of chronic signaling	Reduced inflammatory bone loss	Huang <i>et al.</i> ⁹ , Newman <i>et al.</i> ²³ , Li <i>et al.</i> ³⁰ , Jung <i>et al.</i> ³¹
Hydrogel or scaffold-based drug delivery	Site-specific sustained release	Control of pathway activity	Reduced systemic adverse effects	Newman <i>et al.</i> ²³ , Li <i>et al.</i> ³⁰ , Jung <i>et al.</i> ³¹
Staged implant loading	Reduction of biomechanical stress	Prevents prolonged inflammatory activation	Improved implant survival	Newman <i>et al.</i> ²³ , Insua <i>et al.</i> ²⁹

Future developments will probably focus on "smart" biomaterials that will have the ability to respond in real-time to localized concentrations of specific cytokines, thus self-regulating NF- κ B activity during the healing process³⁰. The use of single-cell transcriptomics and spatial proteomics to map the peri-implant immune microenvironment will allow for an unprecedented resolution of the immune landscape, thus enabling highly individualized approaches to implant selection and the provision of adjunctive therapies⁸.

Clinical trials designed to provide evidence of the efficacy of localized NF- κ B modulators, M2 polarizing coatings and staged biological protocols in compromised hosts will be necessary for related information into routine standard care^{9,17,21,23}.

DISCUSSION

The main concept behind this critique is that NF- κ B signaling serves as an overarching biological mechanism, acting as a master switch that controls whether inflammation converts to typical bone regeneration or deteriorates into chronic disease or infection, ultimately leading to implant failure^{8,14,21,23,29}. Within the specialized ecology of the oral cavity, an environment with an incredible number of microbes, dynamic mechanical loading occurring regularly

and a high degree of tissue regeneration, the speed and level at which NF- κ B is anticipated to be activated, combined with the physiology of the surrounding cells when activated, create critical factors that are directly attributable to the clinical outcome^{1-4,6,8,14,21,23} (Table 3). Recognizing this pathway will help us move forward in the practice of oral surgery from purely mechanical forms of treatment to a combination of immunological and biological methods, requiring a controlled inflammatory response to be involved²¹.

Due to NF- κ B's dual role in regulating bone physiology, it plays a crucial role in regulating alveolar homeostasis; following loss of a tooth, periodontal surgery, or placement of an implant, a short-term elevated level of NF- κ B is the expected and, because of its biological role, required outcome^{6,8,14,23}. The elevation of NF- κ B during the initiation of healing responses after an operative procedure includes attracting early immune cells to the area of surgical tissue trauma, clearing the operative area of necrotic tissue, stimulating the formation of new blood vessels and starting the cascade of events that lead to healing the tissue(s) affected by surgery^{4,6,8}. However, when surgical trauma is too great, the presence of bacterial biofilm remains intact, or biomechanical loading disrupts the sequence of healing, NF- κ B activation may become sustained and cause macrophages to change to a predominantly pro-inflammatory

Table 3: Factors influencing NF- κ B signaling and their biological and clinical effects on oral surgical outcomes

Factor	Effect on NF- κ B signalling	Biological consequences	Potential clinical outcome	Key references
Surgical trauma	Excessive activation	Increased DAMP release and prolonged inflammation	Delayed healing and reduced osseointegration	Zhao <i>et al.</i> ⁴ , Kaushal <i>et al.</i> ¹⁶ , Newman <i>et al.</i> ²³ , Insua <i>et al.</i> ²⁹
Bacterial biofilm	Persistent activation	Chronic cytokine production and osteoclastogenesis	Peri-implantitis and crestal bone loss	Vanlancker <i>et al.</i> ¹ , Rajasekaran <i>et al.</i> ² , Chen <i>et al.</i> ⁶ , Guo <i>et al.</i> ⁸ , Boyce and Xing ¹⁸ , Newman <i>et al.</i> ²³
Diabetes mellitus	Chronic activation via AGE-IKK signaling	Impaired tissue repair and graft	Delayed socket healing consolidation	Zhao <i>et al.</i> ⁴ , Chen <i>et al.</i> ⁶ , Guo <i>et al.</i> ⁸ , Alrabiah <i>et al.</i> ²⁶
Smoking	Sustained M1 macrophage polarization	Oxidative stress and impaired angiogenesis	Increased implant complications	Newman <i>et al.</i> ²³ , Caliri <i>et al.</i> ³²
Hyperlipidaemia	Enhanced inflammatory signaling	Reduced osteoblast activity and increased bone resorption	Compromised osseointegration	Koutsoupiou <i>et al.</i> ²⁷
Estrogen deficiency	Increased NF- κ B activity	Enhanced osteoclast function and bone loss	Increased peri-implant bone resorption	Maruyama <i>et al.</i> ³³
Optimised implant surfaces	Controlled activation and enhanced resolution	M2 macrophage polarization and regenerative signaling	Improved bone-to-implant contact	Ma and Hottiger ¹⁴ , Shirazi <i>et al.</i> ¹² , Newman <i>et al.</i> ²³ , Hotchkiss <i>et al.</i> ²⁴ , Rallis <i>et al.</i> ²⁸ , Li <i>et al.</i> ³⁰ , Emam <i>et al.</i> ³⁴ , Mukaddam <i>et al.</i> ³⁵

cellular phenotype, increase the activity of osteoclastic cells via RANKL and inhibit both osteoblastic cell differentiation and matrix mineralization^{6,8,14,18,20,23,29}. All of these biological events seen clinically would suggest that the body's ability to accelerate the process of resorbing the extracted tooth socket, providing sufficient integration of the bone graft and ultimately allowing for continued loss of bone around an implant have resulted as a direct consequence of the persistent activation of the NF- κ B pathway^{4,6,8,9,14,18,20,23,29}. This pathway's ability to enhance bone resorption and inhibit bone formation provides clinical justification, supporting that regulation of NF- κ B signaling is of greater importance.

In an animal model of peri-implantitis, topical administration of nt-p65-TMD PTD resulted in NF- κ B inhibition and preservation of crestal bone in treated rats, with significantly higher amounts of crestal bone than the control group ($p < 0.05$)³¹. These results indicate that overactivation of NF- κ B may be involved in causing inflammatory bone loss around implants and that preventing the further overactivation of NF- κ B via targeted (localized) intervention may help maintain the peri-implant bone surrounding implants in cases of peri-implant bone loss due to inflammatory disease^{9,23,31}. Modern assessment methodologies emphasize that objective clinical parameters

must be combined with biological data to confidently document when stable osseointegration has overridden inflammatory bone loss²⁵.

The practical application of these genetic realities for oral surgeons relating to clinical management is the use of minimally invasive surgical techniques (i.e., manipulation of the biology) as a primary intervention to ultimately change the level of NF- κ B activity. The preparation of a conservative osteotomy, appropriate constant irrigation, controlled insertion torque and appropriate handling of the soft tissue can all contribute to limiting the surgical trauma inflicted on the bone-implant interface, thereby supporting a more positive early healing process^{4,29}. In addition, the choice of implant surface and adjunctive biomaterial will influence the inflammatory response of the peri-implant tissue and not merely provide mechanical anchorage for the attachment of an implant²¹. For example, hydrophilic, micro-nano-roughened titanium implant surfaces and bioactive coatings will influence the population of peri-implant macrophages toward a pro-regenerative phenotype and thereby decrease excessive NF- κ B activation while maintaining the early, important functions of NF- κ B²⁴. In order for GBR procedures involving barrier membranes and scaffold architecture to function effectively, they must be designed with consideration of the

timeline for inflammation so that they can contribute to a regenerative microenvironment instead of a chronically stimulated one that leads to pathological resorption and inhibits the formation of new bone^{23,30,31}.

In patients undergoing surgery in the oral cavity, systemic conditions that are often observed can lower the threshold for NF- κ B dysregulation^{6,8,23}. Patients with uncontrolled diabetes will have an increased accumulation of advanced glycation end-products that generally activate I κ B kinase (IKK) complexes and chronically may impair socket healing and graft consolidation²⁶. Heavy smokers create oxidative stress and impair microvascular circulation that could maintain a dominance of pro-inflammatory macrophages, delaying transition to tissue repair³². Systemic metabolic disturbances such as hyperlipidemia may increase oxidative stress and thereby impair osteoblast function, favor bone resorption and compromise both bone regeneration and implant osseointegration²⁷. Emerging evidence indicates that statins may favor dental implant osseointegration by modulating molecular pathways, including NF- κ B inhibition, thereby potentially supporting bone formation and healing²⁸. Individuals who have a history of severe periodontitis or those on long-term anti-resorptive medications commonly present with primed immune niches in which NF- κ B signaling cannot resolve appropriately, thus increasing the probability of developing peri-implantitis or denuded bone²³. Before surgery, preoperative optimization including glycemic stabilization, periodontal decontamination and cessation of tobacco use will decrease baseline inflammation and permit a normal physiological transition of cytokine signaling in NF- κ B throughout the process of regeneration²³. Furthermore, addressing metabolic insufficiencies at a mitochondrial level may prove essential, as disruptions in mitochondrial DNA and the resulting activation of the cGAS-STING-NF- κ B axis further exacerbate the inflammatory burden in susceptible tissues⁸.

Although it seems reasonable to consider pharmacological suppression of NF- κ B in high-risk surgical patients, total inhibition of that pathway is clinically counter-productive²³. NF- κ B is essential for antimicrobial defense, epithelial closure and early wound vascular ingrowth¹³. Total inhibition will inevitably lead to an increased risk of post-operative infection and delayed healing of soft tissues²³. The evolving therapy paradigm is thus focused on precise modulators rather than total inhibitors. Localized delivery of pharmacologic agents such as decoy oligodeoxynucleotides, natural bioflavonoid modulators or targeted cytokine biologics can provide significant promise for selectively reducing chronic signaling at the implant interface while not compromising systemic immunity³⁰.

Next-generation biomaterials have been developed to selectively release immunomodulatory ions or peptides over time to create a highly practical means of aligning material science with biological timelines for oral wound healing³⁰.

Translating NF- κ B biology into clinical guidelines and everyday care encounters obstacles that stem from the significant cross-talk between the NF- κ B signaling pathway and other biological pathways, such as Wnt, MAPK and other pathways related to metabolism, which can lead to compensatory outgrowths that may affect healing^{8,14}. Additionally, there is a significant amount of variability among patients in their genetic polymorphisms, immune status and oral microbiome; therefore, these factors create individual "healing landscapes" for each patient^{1,2,8,15}. Future advancements in clinical practice will occur as a result of (i) High-resolution mapping of the immune niches surrounding implants^{8,14,15}, (ii) The development of chair-side biomarkers that predict dysregulation of NF- κ B prior to radiographic evidence of bone loss^{6,23,30} and (iii) Robust clinical trials using localized immunomodulatory adjuvants in patients with bone-compromised conditions^{9,21,30,31}. Furthermore, the incorporation of artificial intelligence into surgical planning and material selection will enable clinicians to provide personalized implant care based on the inflammatory risk for each individual patient^{8,14,15,30}.

Ultimately, the long-term viability of modern oral surgery will depend on an understanding of inflammation as a biological facilitator rather than a biological adversary that must be eliminated^{4,6,13,23}. By aligning surgical procedures, biomaterials and patient management with the natural kinetic response of NF- κ B signaling, clinicians will be able to convert a pathway that has previously been associated with pathological bone loss into a predictable mechanism for enhancing osseointegration and achieving long-term stability in a clinical setting. The future of oral surgical practice will rely heavily on integrating immunological and biological processes through the implementation of physiologically modulated NF- κ B in regenerative dental implant therapy and predictable alveolar bone reconstruction.

The concentration of estrogen in women has an important impact on inflammation and osteogenic processes. For instance, estrogen deficiency can result in prolonged proinflammatory state which tends to enhance osteoclast activity, impair the action of osteoblasts and finally completely inhibit efficacious bone regeneration³³. Therefore, consideration of hormonal status and the interactions between NF- κ B and Wnt pathways during preoperative risk assessment and treatment planning for oral regenerative procedures is also important. In order for the oral surgeon to achieve predictable healing the NF- κ B and Wnt

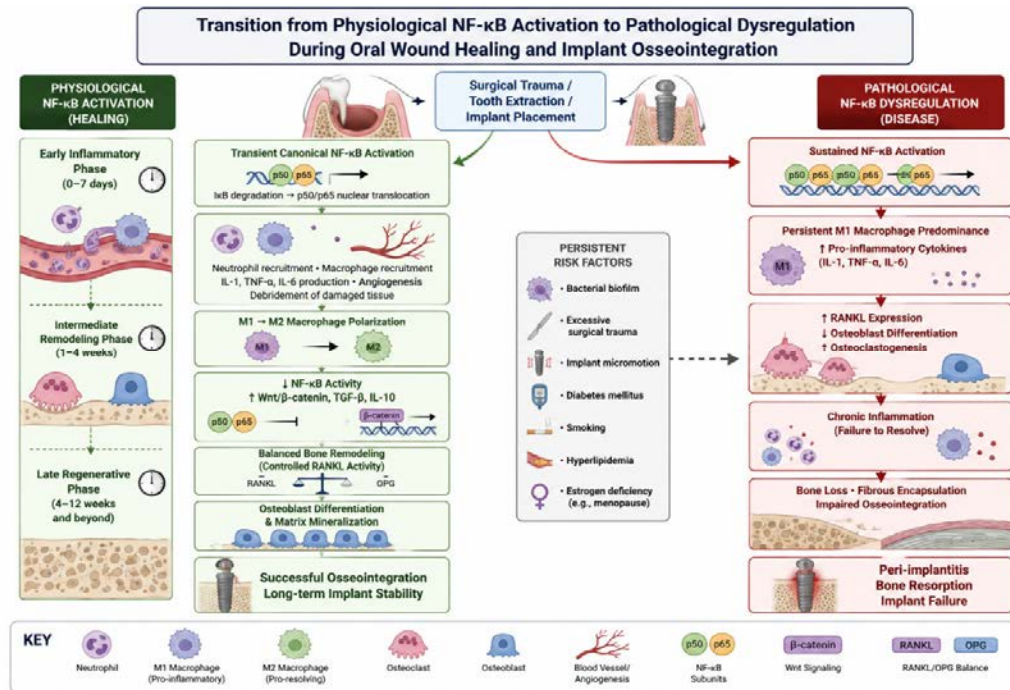


Fig. 1: Schematic illustration of the transition from physiological NF- κ B activation during tissue healing to pathological dysregulation associated with chronic inflammation, impaired bone remodeling and peri-implant complications

pathways must be coordinated through the antagonistic nature of crosstalk between each pathway, which is critical when transitioning from initial inflammation phase to late bone formation phase; specifically, these phases require a transition of signaling from NF- κ B to Wnt-oriented activity³⁴. The current evidence showed that although the use of zirconia as a dental implant has been viewed to have great biocompatibility, this material does, in fact, induce an NF- κ B response, similar to titanium, via TNF- α stimulation in MG-63 cells, suggesting that the initial inflammatory response induced by both materials at the molecular level is comparable³⁵ (Fig. 1).

CONCLUSION

The NF- κ B signaling pathway acts as a regulatory mechanism that is responsible for the smooth transition between physiological tissue repair and pathophysiological destruction in oral surgery. Activation of the NF- κ B pathway transiently promotes the initiation of the surgery. In chronic inflammatory cases, uncontrolled activation of the NF- κ B pathway results in the production of RANKL by osteoblasts, which consequently leads to bone loss. Therefore, the main goal of oral surgical procedures is not to block the NF- κ B signaling pathway completely but to regulate the signaling

profile during surgery over time. This will allow the surgeons to control the inflammatory process and thus achieve optimal and predictable performance.

SIGNIFICANCE STATEMENT

The present review fills a major gap in the current literature, synthesizes fragmented information from immunology, bone biology and implantology and formulates a new phase of NF- κ B signaling in oral surgery based on kinetics. The study departs from the conventional approach of viewing inflammation merely as a biological enemy and argues that NF- κ B is not to be inhibited totally but needs to be skillfully modulated with the help of timely control over its activity, which ensures fast activation during the healing process and deactivates the mechanisms of inflammation and healing when it comes to the processes of bone regeneration. In practical terms, this study translates the molecular interactions into strategies that can be used in practice, explaining how minimally invasive surgical aids, immunoresponsive biomaterials and local pharmaceuticals can be effective for macrophage polarization, achieving osseointegration and preventing peri-implantitis. The review represents a shift in the paradigm of oral surgery from purely mechanical to immunologically grounded practice.

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