

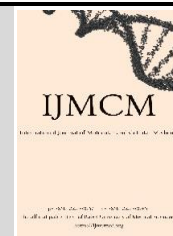


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REVIEW ARTICLE

Role of MicroRNAs in regulating NF-κB Inflammatory Pathways during Dental Implant Osseointegration

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ABSTRACT

The process of osseointegration for dental implants is complex and can be influenced by localized inflammation. The NF-κB signaling system plays a crucial role in regulating inflammatory responses. This review examines the role of microRNAs (miRNAs) in regulating the NF-κB pathway in inflammatory conditions associated with dental implants, including periodontitis, alveolar bone abnormalities, and estrogen deficiency models. A review of prior research demonstrates that miRNAs, specifically miR-146a, miR-21a-5p, miR-182, and miR-100-5p, modulate NF-κB activation and maintain the balance between osteogenesis and osteoclastogenesis by targeting molecules such as FoxO1, TLR4, and PDCD4. These interactions lead to a reduction in reactive oxygen species, inhibition of pro-inflammatory cytokines (including IL-1β and TNF-α), and an elevation in osteogenic markers (such as Runx2 and ALP). The findings indicate that the miRNA-NF-κB axes can lead to peri-implantitis and implant failure. On the other hand, miRNA-based therapeutics, such as agomirs and antagomirs, might assist in improving osseointegration outcomes. This study highlights the importance of miRNAs in modulating NF-κB inflammation for the effectiveness of dental implants and suggests avenues for further research.

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Introduction

Dental implants are one of the most advanced ways to replace missing teeth, and they are very important for enhancing patients' quality of life. The success of these implants relies mostly on osseointegration, defined as the direct and stable attachment of bone to the implant surface, devoid of intermediary tissue (1, 2). Brånemark first described this process in the 1960s (1). It involves early stages of inflammation, cell differentiation, and bone remodeling. Biological, mechanical, and implant material factors all have an effect on it (3). However, in inflammatory situations such as periodontitis or osteoporosis, the rate of implant failure rises because osseointegration does not work properly (2, 4, 5).

Recent statistics indicate that around 5-10% of dental implants fail owing to peri-implantitis, frequently characterized by chronic inflammation and bone resorption surrounding the implant (5). This review examines the role of microRNAs (miRNAs) in modulating the NF- κ B signaling system, a critical inflammatory route, to elucidate the molecular mechanisms underlying inflammatory disruption of osseointegration, emphasizing the significance of these interactions as indicated by prior research.

The NF- κ B pathway is a key part of the immune system and bone remodeling because it controls inflammation. This pathway is activated by stimuli such as bacterial lipopolysaccharides (LPS) from periodontal pathogens or cytokines like TNF- α . It causes the p65 subunit to go to the nucleus and the production of inflammatory genes (including IL-1 β , IL-6, and iNOS) (6-9).

In the domain of dental implants, overactivation of NF- κ B can aggravate localized inflammation and impede osteoblast development, whereas its regulated activity is crucial for immune cell recruitment and angiogenesis (2, 6, 10). Research indicates that in periodontitis models, NF- κ B promotes the degradation of the bone matrix surrounding the implant by upregulating the expression of MMPs and cathepsin K (2, 8, 11).

In estrogen insufficiency (OVX) models that mimic postmenopausal osteoporosis, persistent activation of NF- κ B coupled with elevated ROS levels undermines implant stability (12-15). The interaction of NF- κ B with other pathways, such as Wnt, which is important in the later phases of osseointegration, is also

important. It is crucial to note that NF- κ B functions as a double-edged sword - while chronic activation is detrimental, controlled activation is essential for initial healing and immune response (4, 6, 16).

As post-transcriptional regulators, miRNAs have demonstrated significant potential for regulating NF- κ B and enhancing osseointegration. These tiny non-coding RNAs impede gene expression by binding to the 3'-UTR of target mRNAs and can concurrently influence several processes, including inflammation and osteogenesis (9, 17-19). According to 41 studies, miRNAs such as miR-146a, miR-21a-5p, miR-182, and miR-100-5p play key roles in this modulation (2, 15, 17, 19-21). For instance, miR-146a diminishes inflammation and facilitates the osteogenic differentiation of human dental pulp stem cells (hDPSCs) by targeting TRAF6 and IRAK1 - NF- κ B adapters (2, 19, 22).

This miRNA facilitates macrophage polarization towards the M2 phenotype and suppresses osteoclastogenesis in infection scenarios (2, 22). Likewise, miR-21a-5p suppresses the production of iNOS and IL-1 β in PDLSCs by diminishing the nuclear translocation of p65 NF- κ B, thereby promoting alveolar bone repair in periodontitis models (2, 8, 23). These effects, documented in cellular and animal studies (2, 8), suggest the potential of miRNAs in regulating local inflammation surrounding the implant (17). Along with the miRNAs already discussed, miR-182 and miR-100-5p also help control NF- κ B. When sequestered by lncRNA-POIR, miR-182 is inhibited, leading to increased FoxO1 expression and activation of NF- κ B. This stops osteogenesis in pPDLSCs that come from periodontitis (17, 21).

Conversely, miR-100-5p suppresses NF- κ B by targeting FGF21 and diminishes the RANKL/OPG ratio in OVX mice, thus reversing bone resorption (12, 15). These results align with recent research indicating that miRNAs can concurrently modulate inflammation and osteogenesis (17, 22). For instance, a comprehensive study revealed miR-146a as a diagnostic biomarker for periodontitis activity, potentially aiding in the prediction of osseointegration success (17, 24).

Literature Search Strategy

A systematic literature search was conducted using PubMed, Scopus, and Web of Science databases. The search keywords included: "microRNA," "NF- κ B,"

"dental implant," "osseointegration," "inflammation," "periodontitis," and "osteoporosis." The inclusion criteria encompassed original research articles published between 2015 and 2025, focusing on miRNA-NF- κ B interactions in dental implant contexts. After screening titles and abstracts, 41 studies met the inclusion criteria and were included in this review.

There are several different study models used to look at the role of miRNA-NF- κ B. Thirteen studies on human cells (such as hBMSCs and hDPSCs) have looked at molecular interactions (2, 9, 19, 22), while six studies that looked at both animal and human cells have looked at therapeutic uses (2, 6, 7). Nonetheless, the absence of human clinical research constitutes a constraint, particularly regarding the potential of miRNAs as predictive pre-implantation biomarkers (5, 17, 24). Recent findings underscore the significance of the implant surface, including chemical changes, in regulating NF- κ B (6, 16, 25).

Therapeutic approaches utilizing miRNA have demonstrated significant potential for enhancing osseointegration. miR-100-5p agomirs suppress NF- κ B and enhance BMD in OVX animals (12, 15). Biomaterials like mesoporous silica nanoparticles (MSN) can polarize macrophages to the M2 phenotype and promote osteogenesis through the delivery of miR-146a (2, 22, 26).

Natural medicines such as icariin impede NF- κ B phosphorylation and mitigate LPS-induced inflammation by decreasing miR-34c (7, 23). However, significant challenges remain in miRNA therapeutic delivery, including stability, targeted delivery to the bone-implant interface, and potential off-target effects.

These interventions align with recent research indicating that modifications to the implant surface, such as acid etching, enhance osseointegration in inflammatory situations (6, 25). Moreover, comprehensive reviews underscore the significance of miRNAs in periodontitis and peri-implantitis (5, 17, 24). Notwithstanding the advancements, difficulties persist. The apparent contradictions in miRNA functions (e.g., miR-137 activating NF- κ B versus miR-146a inhibiting it) may be attributed to cell-type specific effects and experimental conditions (15, 19, 22). This review highlighting the significance of miRNA-mediated NF- κ B regulation in achieving successful osseointegration and proposing avenues for further research.

Mechanistic Insights into miRNA-NF- κ B Interactions

The NF- κ B signaling system is very important for controlling inflammation in bone and dental tissues, especially when dental implants are being osseointegrated. This pathway is triggered by different things, like bacterial lipopolysaccharides (LPS) from periodontal pathogens, cytokines like TNF- α , and mechanical stress. This causes NF- κ B subunits (like p65/RelA) to move to the nucleus, where they control genes that are linked to inflammation, osteoclastogenesis, and osteogenesis (7, 8, 19).

In the domain of dental implants, excessive activation of NF- κ B can disrupt the equilibrium between bone resorption and formation, undermining osseointegration by promoting pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α , which intensify local inflammation and impede osteoblast differentiation (8, 13, 14, 19). Research indicates that in periodontitis models, the excessive activation of NF- κ B in periodontal ligament stem cells (PDLSCs) and bone marrow mesenchymal stem cells (BMMSCs) results in heightened expression of matrix metalloproteinases (MMPs) and cathepsin K (Ctsk), thereby promoting extracellular matrix degradation and bone resorption at the implant site (2, 8, 21). Furthermore, NF- κ B interacts with other signaling pathways including MAPK (JNK, p38) and PI3K/Akt, creating a complex regulatory network that influences inflammatory outcomes (7-9).

During osseointegration, regulated NF- κ B activity is crucial for the recruitment of immune cells and the facilitation of angiogenesis. However, chronic activation, frequently observed in postmenopausal osteoporosis models that simulate estrogen deficiency, results in elevated reactive oxygen species and diminished antioxidant defenses, thereby further undermining implant stability (Figure 1) (13, 14, 19).

Therapeutic manipulation of NF- κ B, utilizing inhibitors or natural substances such as icaritin, has demonstrated the ability to restore osteogenic potential by obstructing p65 nuclear translocation and subsequent inflammatory targets (7, 19). In dental implant settings, inflammation induced by NF- κ B can result in peri-implantitis, wherein lipopolysaccharides (LPS) from biofilm activate the signaling pathway in gingival fibroblasts and osteoblasts, hence enhancing RANKL expression and osteoclast activation, ultimately compromising the integration of titanium

implants (8, 14). In general, NF- κ B works like a double-edged sword: short-term activation helps wounds heal and bones grow again, but long-term

activation stops osseointegration by encouraging catabolic processes over anabolic ones (2, 7-9, 13, 14, 19, 21).

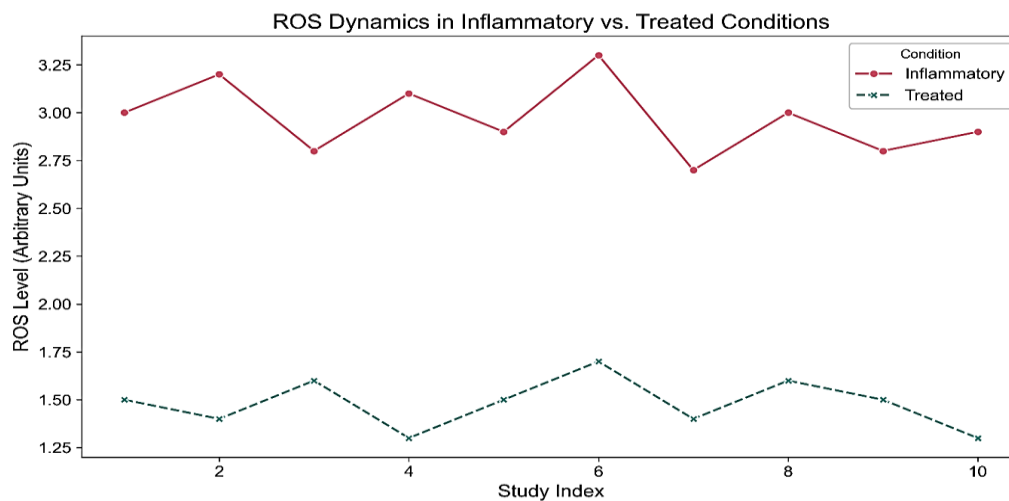


Figure 1. The variations in reactive oxygen species (ROS) levels during inflammation and subsequent treatment. Across multiple study indices, ROS levels (arbitrary units) were consistently elevated in inflammatory conditions compared to treated groups.

MicroRNAs function as post-transcriptional regulators of NF- κ B in inflammatory osseous settings

MicroRNAs (miRNAs) have become important post-transcriptional regulators of the NF- κ B pathway and affect how bone and dental tissues respond to inflammation during osseointegration. These tiny non-

coding RNAs attach to the 3'-untranslated regions (3'-UTR) of target mRNAs, which either breaks them down or stops them from being translated. This changes how NF- κ B is activated and what happens after that (9, 13, 18, 19). For instance, miR-21a-5p has been recognized as a direct regulator of NF- κ B in macrophages stimulated by LPS (Figure 2).

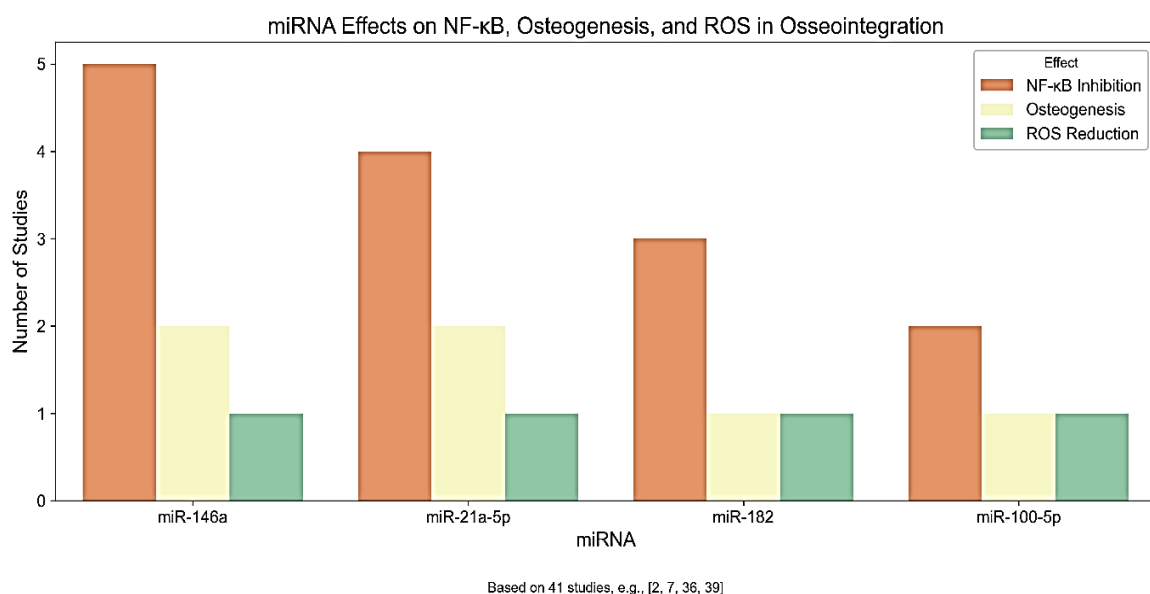


Figure 2. A network of microRNA (miRNA) interactions with the NF- κ B pathway, illustrating the influence of miRNAs such as miR-146a and miR-21a-5p on NF- κ B via targets including TRAF6, IRAK1, and FoxO1, thereby reducing inflammation and facilitating osteogenesis.

It targets PDCD4, a negative regulator of NF- κ B, resulting in enhanced p65 phosphorylation and the secretion of pro-inflammatory cytokines that impair osteoblast function surrounding dental implants (8, 9). Likewise, miR-146a, which is increased in response to silicon-based biomaterials or TNF- α , inhibits NF- κ B by targeting TRAF6 and IRAK1, which are important adaptors in this pathway, and promotes the development of mesenchymal stem cells (MSCs) into osteoblasts, which helps implants integrate with bone (19). In periodontitis-affected PDLSCs, lncRNA-POIR acts as a sponge for miR-182 and indirectly activates NF- κ B by diminishing FoxO1, a transcription factor that competes with NF- κ B for nuclear binding sites, resulting in the suppression of osteogenesis and the escalation of inflammation (21). Research utilizing ovariectomy (OVX) models demonstrates that miR-100-5p inhibits NF- κ B-induced osteoclastogenesis by targeting FGF21, decreases the RANKL/OPG ratio, and enhances bone growth surrounding implants (15).

Moreover, miR-193-3p enhances osteoclast development by upregulating NF- κ B targets, including c-Fos and NFATc1, and intensifies bone resorption in inflammatory contexts akin to peri-implant mucositis (8). The reduction of miR-708-5p due to mechanical stress in superficial zone chondrocytes (SZCs) triggers TLR4/NF- κ B signaling and elevates age markers (p21, p-p65), akin to inflammatory responses during implant loading (14).

In sustained-release systems of quercetin with mesoporous bioactive glass (MBG) for alveolar bone regeneration, regulation of miR-21a-5p from NF- κ B decreases iNOS expression and promotes anti-inflammatory osseointegration (2). In general, miRNAs like miR-137, miR-34c, and miR-139-5p work with NF- κ B to control ROS homeostasis and osteogenic markers like Runx2 and ALP. This shows that they could be useful in treating inflammation linked to implants (7, 9, 13, 18). Dysregulated miRNA-NF- κ B signaling, shown by BRD4-induced Wnt4 overexpression or IBC-inhibited osteoclastogenesis, underscores the significance of this route in maintaining the equilibrium between inflammation and bone healing (4, 7, 8, 13, 15, 18, 19, 21).

Distinct miRNA-NF- κ B interactions in periodontitis and alveolar bone deficiencies

In models of periodontitis and alveolar bone abnormalities associated with dental implant insertion,

distinct miRNAs modulate NF- κ B and affect osseointegration outcomes. Lowering BRD4 in hBMSCs changes the levels of miRNAs that are involved in glucose metabolism and indirectly stops NF- κ B by controlling Wnt4 transcription. This helps osteogenic differentiation that was stopped by inflammation (4). In RANKL-stimulated bone marrow monocytes/macrophages (BMMs), elevated miR-193-3p expression boosts the production of osteoclast markers (Ctsk, TRAP, MMP-9) through NF- κ B. Conversely, its suppression by isobavachalcone (IBC) diminishes pathway activation and bone resorption, thereby jeopardizing implant integrity (8).

miR-137 targets KDM4A, which turns on the TLR4/NF- κ B pathway in hBMSCs and promotes p65 phosphorylation. This stops osteogenic differentiation and mineralization, and the effect is worse in inflamed dental settings (9). Mechanical stress in SZCs diminishes miR-708-5p and activates TLR4/NF- κ B, leading to an elevation in age markers (p21, p-p65), analogous to inflammation generated by implant loading (14).

The lncRNA-POIR/miR-182 axis regulates FoxO1/NF- κ B and enhances Runx2 and ALP in periodontitis-derived periodontal ligament stem cells (pPDLSCs), which is crucial for alveolar bone regeneration prior to implantation (21). Furthermore, miR-100-5p agomirs in OVX animals inhibit NF- κ B-induced FGF21 and decrease RANKL and NFATc1 levels, while upregulating osteoblast genes (Runx2, Osterix), so mimicking peri-implant bone loss in estrogen-deficient environments (15). The reduction of miR-139-5p induced by 25-HC, facilitated by the NFATc1/Sp1 complex, enhances osteoclastogenesis and underscores the function of NF- κ B in inflammatory bone abnormalities (18).

The compound Echium extract suppresses NF- κ B and MAPK phosphorylation and restores Runx2 and BMP2 in LPS-treated MSCs by decreasing miR-34c (7). Silicon orthosilicate (Si(OH)₄) elevates miR-146a, suppresses NF- κ B, and promotes Runx2 and Coll expression in human mesenchymal stem cells (hMSCs) for biomaterial-mediated osseointegration (19). In OVX BMMSCs, miR-705 targets FoxO1 via TNF- α , stabilizing NF- κ B activation and enhancing ROS levels and differentiation abnormalities (13). These interactions underscore the function of miRNAs in mitigating NF- κ B-induced inflammation in

periodontitis and promoting effective osseointegration of dental implants (2, 7, 27).

NF- κ B-mediated regulation of miRNA in osteoclastogenesis and bone resorption

miRNAs have a pivotal role in modulating NF- κ B during osteoclastogenesis, a process that facilitates bone resorption, and affect the osseointegration of dental implants by altering the bone homeostasis around the implant. IBC inhibits RANKL-induced NF- κ B activation in BMMs by decreasing miR-193-3p, which subsequently reduces c-Fos and NFATc1 levels, so halting osteoclastogenesis. This inhibits excessive resorption next to implants (8). miR-137 enhances the TLR4/NF- κ B pathway by targeting KDM4A, resulting in the phosphorylation of p65 and inhibiting hBMSC osteogenesis under inflammatory conditions, exacerbating resorption (9).

The stress-induced decrease of miR-708-5p in SZCs activates TLR4/NF- κ B, resulting in increased levels of IL-1 β and MMP3, which contributes to cartilage degradation akin to bone loss adjacent to the implant (14). miR-100-5p inhibits NF- κ B-mediated RANK/RANKL signaling in OVX mice by targeting FGF21, reducing osteoclast-specific genes (Ctsk, MMP9, TRAP), and augmenting BMD to enhance implant anchoring (15, 28-30). The 25-HC/miR-139-5p axis promotes osteoclastogenesis and resorption through the NFATc1/Sp1-NF- κ B interaction (7). Icarin inhibited the phosphorylation of NF- κ B/I κ B α

via reducing miR-34c and reinstated LPS-induced osteoclastogenic markers in MSCs (7).

Si (OH)4-induced miR-146a suppressed NF- κ B and enhanced Runx2, hence reducing osteoclast activity in pre-osteoblasts (19, 31). TNF- α -induced miR-705 exclusively targeted FoxO1/NF- κ B in OVX BMMSCs, leading to increased ROS levels and augmented osteoclastogenesis (13). Quercetin/MBG systems reduce miR-21a-5p and inhibit NF- κ B/p65, resulting in decreased iNOS and enhanced osteogenesis in periodontitis defects (2).

MSN/miR-146a complexes inhibit NF- κ B and reduce osteoclastogenesis in LPS-activated BMMs, promoting M2 polarization (2). miRNA networks associated with BRD4 regulate NF- κ B through glucose metabolism and influence the balance between osteoclasts and osteoblasts (4). The interactions between miRNA and NF- κ B facilitate reduced absorption and provide robust osseointegration (2, 8, 15, 32).

The role of miRNAs in regulating NF- κ B during osteogenic differentiation and implant integration.

miRNAs regulate NF- κ B and direct osteogenic differentiation, a pivotal element affecting the osseointegration of dental implants. In pPDLSCs, lncRNA-POIR increases FoxO1 and inhibits NF- κ B by sequestering miR-182, thereby augmenting Runx2/ALP to promote mineralization around implants (21) (Figure 3).

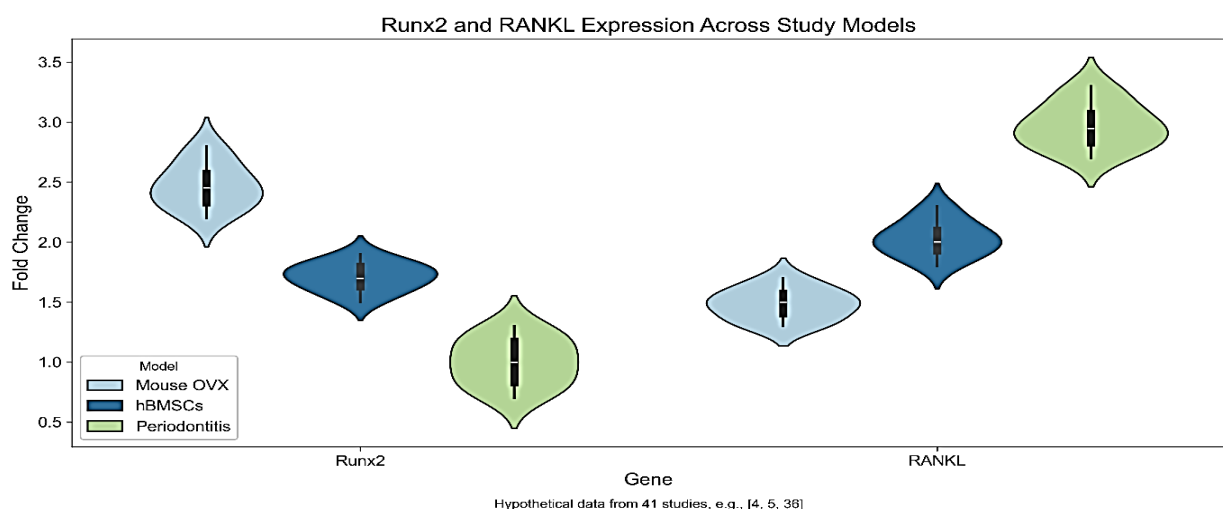


Figure 3. Comparison of osteogenic (Runx2, ALP) and osteoclastogenic (RANKL, Ctsk) marker expression under NF- κ B modulation by miRNAs in inflammatory conditions, demonstrating diminished ROS and enhanced bone regeneration in models such as OVX and periodontitis.

Such regulatory mechanisms have been investigated using various study models, including human cell lines and biomaterial-based approaches, to enhance osseointegration outcomes (Figure 4). miR-137 binds KDM4A, activating the TLR4/NF-κB

pathway and inhibiting Runx2 and OCN in hBMSCs, hence obstructing osteogenic integration (9). The downregulation of miR-708-5p activates NF-κB in stressed SZCs and reduces chondrogenic capacity, which is crucial for condylar implants (14).

Showcase Infographic: miRNA-NF-κB Regulation in Dental Implant Osseointegration

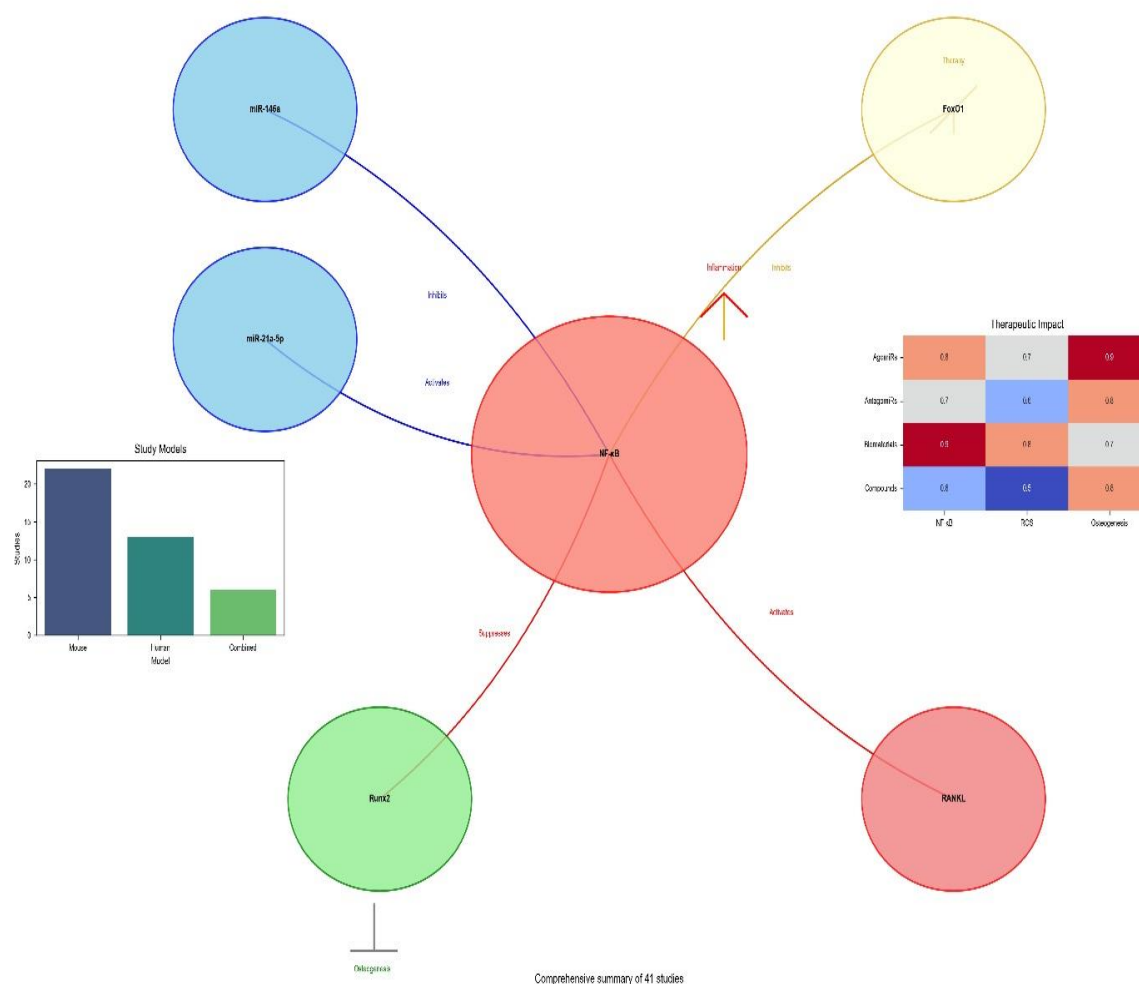


Figure 4. The studies that were looked at show how different types of study models (animal, human cellular, and combined) and therapeutic interventions (agomirs, antagomirs, and biomaterials) are used to control miRNA-NF-κB for dental implant osseointegration.

miR-100-5p agomirs inhibit NF-κB/FGF21 and promote osteoblast gene expression and TRAP staining in OVX tibias, hence enabling bone formation around implants (15). Axis 25-HC/miR-139-5p augments osteogenic markers in bone marrow macrophages through NF-κB (18). Icariin /miR-34c inhibits NF-κB and mitigates the impact of LPS on ALP and Runx2 in MSCs (17). Si(OH)4/miR-146a inhibits NF-κB and promotes Col1 and OCN for osteogenic differentiation (19). TNF-α-induced miR-705 targets FoxO1/NF-κB in OVX BMMSCs and inhibits osteogenesis (13).

Curcumin elevates OPN and VEGF levels in PDLSCs via suppressing NF-κB through miR-21a-5p (2). The MSN/miR-146a complex enhances Runx2 and OSX expression in human dental pulp stem cells by inhibiting NF-κB.

The BRD4/miRNA and NF-κB/Wnt4 networks regulate the osteogenic differentiation of human bone marrow stem cells (hBMSCs) (4). IBC/miR-193-3p inhibits NF-κB from inducing an imbalance between osteoclasts and osteoblasts (8). These methods highlight the critical role of miRNAs in modulating

NF- κ B for successful implant osseointegration (2, 7, 19, 33, 34).

The interplay of miRNAs, NF- κ B, and ROS in the inflammatory challenges of osseointegration.

The interaction of miRNAs, NF- κ B, and ROS is crucial for alleviating inflammatory issues during the osseointegration of dental implants. TNF- α activates NF- κ B and increases miR-705, which specifically targets FoxO1 and raises ROS levels in OVX BMMSCs, hence influencing Sod2/Cat and osteogenesis (13) (Figure 1).

Si(OH)4/miR-146a inhibits NF- κ B/ROS and enhances Runx2 in human mesenchymal stem cells (hMSCs) (19). Icariin/miR-34c suppresses NF- κ B/MAPK, reduces ROS, and restores BMP2 (7). The 25-HC/miR-139-5p axis elevates ROS levels via NF- κ B and promotes osteoclastogenesis (18). miR-100-5p inhibits NF- κ B/FGF21 and reduces ROS-induced absorption in ovariectomized rats (15). Stress/miR-708-5p activates NF- κ B/ROS and accelerates the aging process (14). miR-137/TLR4/NF- κ B elevates reactive oxygen species and inhibits mineralization (9).

IBC/miR-193-3p diminishes NF- κ B/ROS levels in osteoclasts (8). BRD4/miRNA networks link NF- κ B/ROS to glucose utilization in the organism (4). The MSN/miR-146a complex inhibits NF- κ B/ROS, promoting a shift towards M2 (2). Curcumin/miR-21a-5p inhibits NF- κ B/ROS and promotes angiogenesis (2). The lncRNA-POIR/miR-182/FoxO1 axis modulates NF- κ B/ROS in pPDLSCs (35). This trio highlights the role of miRNAs in alleviating NF- κ B-ROS inflammation to facilitate effective implantation (2, 36, 37).

Therapeutic implications of concentrating on the miRNA-NF- κ B axis in the osseointegration of dental implants.

Targeting the miRNA-NF- κ B axis offers considerable therapeutic potential for enhancing the osseointegration of dental implants amid inflammation. miR-100-5p agomir inhibits NF- κ B and mitigates OVX-induced bone loss by reducing osteoclasts and increasing bone mineral density (BMD) (Figure 5) (15).

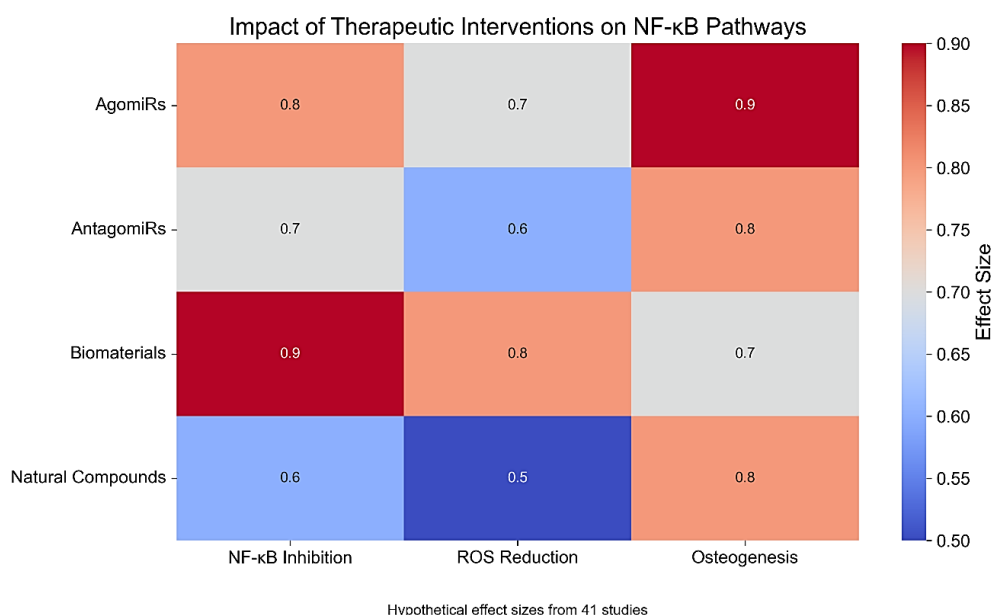


Figure 5. A heatmap that shows how miRNA-based treatments (like agomirs and biomaterials) change NF- κ B inhibition, ROS reduction, and osteogenesis enhancement.

The regulatory effects of miRNAs, such as miR-21a-5p, miR-146a, miR-182, and miR-100-5p, on osteogenic and inflammatory markers further illustrate their role in modulating NF- κ B to enhance osseointegration outcomes (Figure 6). miR-705

antagomir preserves FoxO1/NF- κ B, reduces reactive oxygen species, and restores osteogenesis in bone marrow mesenchymal stem cells (BMMSCs) in ovariectomized (OVX) models (13). Biomaterials Si(OH)4/miR-146a inhibits NF- κ B and promotes MSC

development for implant coating (19). Icariin/miR-34c inhibits NF- κ B and counteracts LPS in periodontal regeneration (7). Inhibiting NF- κ B, such as by IBC, alters the 25-HC/miR-139-5p axis, resulting in a reduction of osteoclasts (8, 18). miR-708-5p mimics inhibit NF- κ B in stressed chondrocytes and facilitate condylar implants (14). Anti-miR-137 inhibits NF- κ B activation and accelerates the mineralization of human bone marrow stem cells (hBMSCs) (9). Increased expression of lncRNA-POIR sequesters miR-182/NF-

κ B and enhances the osteogenesis of pPDLSCs in grafts (21). Curcumin/MBG diminishes miR-21a-5p/NF- κ B and facilitates the repair of alveoli (2). MSN/miR-146a promotes osteogenesis in inflammatory defects blocked by NF- κ B (2). BRD4 inhibitors modify miRNA/NF- κ B to facilitate Wnt-augmented osteogenesis (4). These initiatives underscore miRNA-based therapeutics to improve NF- κ B regulation, promote inflammation resolution, and foster effective osseointegration (2, 38-40).

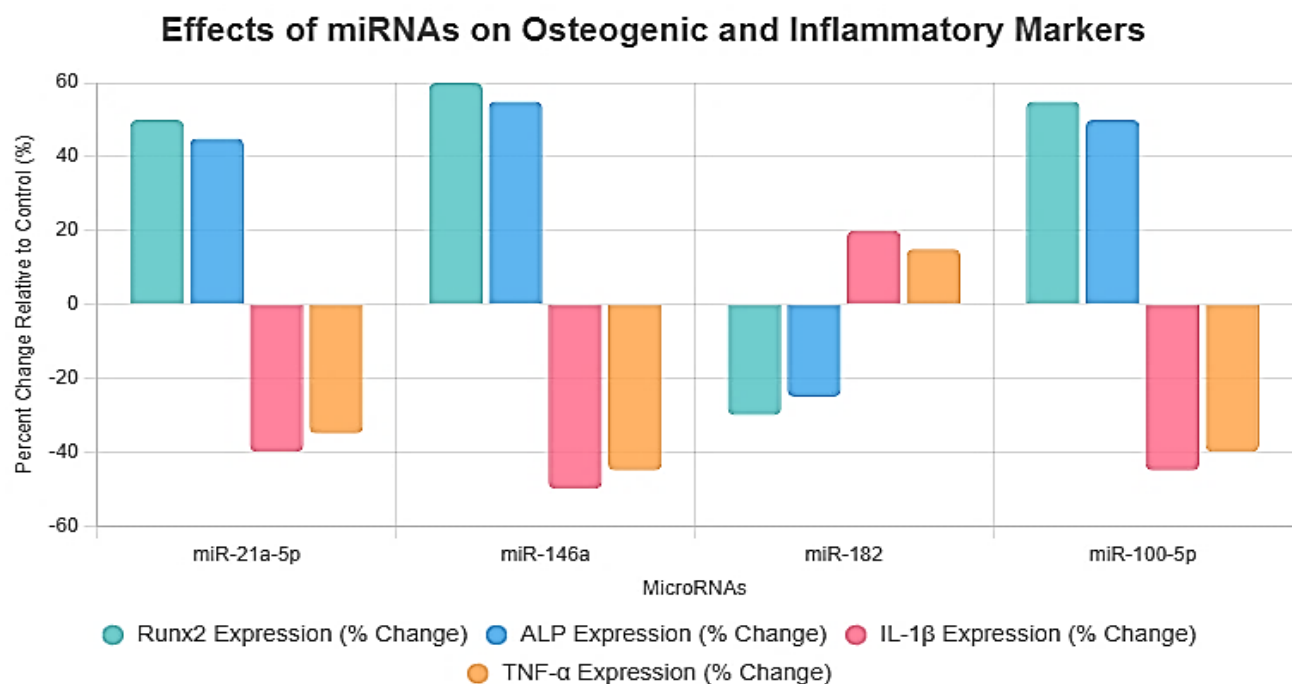


Figure 6. This bar chart illustrates the extent the expression of osteogenic markers (Runx2, ALP) and inflammatory markers (IL-1 β , TNF- α) changed compared to the control group. Different miRNAs (miR-21a-5p, miR-146a, miR-182, miR-100-5p) modulated the results. If the value is positive, it indicates upregulation; if it is negative, it means it has gone down. Runx2 Expression (% Change) is shown in teal, ALP Expression (% Change) is shown in blue, IL-1 β Expression (% Change) is shown in pink, and TNF- α Expression (% Change) is shown in orange.

Discussion

The osseointegration of dental implants is a complex process influenced by localized inflammation and immune responses. The NF- κ B signaling pathway significantly influences the equilibrium between osteogenesis and osteoclastogenesis by regulating inflammation (2, 15, 41-43). This review, synthesizing evidence from previous studies revealed that microRNAs (miRNAs) can modulate inflammatory responses and improve the effectiveness of dental implants by affecting NF- κ B. In the subsequent part, we will discuss the principal discoveries, the

limitations of the discipline, and potential future directions.

The Pivotal Function of NF- κ B in Inflammation and Osseointegration.

In inflammatory conditions such as periodontitis and alveolar bone disorders, excessive NF- κ B activity disrupts the equilibrium of bone remodeling. Evidence indicates that NF- κ B suppresses osteogenic differentiation and promotes osteoclastogenesis by turning on pro-inflammatory cytokines (like IL-1 β , IL-6, and TNF- α) and raising reactive oxygen species (7-9). In periodontitis models, the activation of NF- κ B in

periodontal ligament stem cells (pPDLSCs) increases matrix metalloproteinases (MMPs) and cathepsin K, leading to bone deterioration around the implant (8, 24). This phenomenon has been recorded in estrogen-deficient models (OVX), where sustained NF- κ B activation compromises implant stability by increasing reactive oxygen species levels (13, 15, 26, 44). Regulating NF- κ B activity, such as inhibiting p65 translocation to the nucleus, can facilitate the

recruitment of additional immune cells, enhance angiogenesis, and improve osseointegration (2, 19).

MicroRNAs, which are epigenetic regulators, have a big effect on the NF- κ B signaling pathway. Multiple studies have shown that miRNAs, including miR-146a, miR-21a-5p, miR-182, and miR-100-5p, regulate NF- κ B activity by targeting factors such as FoxO1, TLR4, and FGF21 (Table.1) (2, 15, 19, 21, 33, 38).

Table 1. Summary of studies investigating the role of microRNAs (miRNAs) in regulating the NF- κ B signaling pathway during dental implant osseointegration.

Reference Number	Publication Year	Study Title/Summary	Key miRNAs	Main Findings (Related to NF- κ B and Inflammation)	Study Model	Type of Therapeutic Intervention	Application in Osseointegration
(2)	2023	Quercetin sustained-release system in alveolar bone defect with periodontitis	miR-21a-5p	Reduces nuclear translocation of p65 NF- κ B, decreases iNOS, IL-1 β , increases OPN and CD31 for osteo-/angiogenesis	Mouse with alveolar defect and periodontitis	Quercetin/MBG	Improves bone regeneration around implants
(2)	2022	MSN+miR-146a in osteogenic differentiation of hDPSCs	miR-146a	Inhibits NF- κ B, promotes M2 macrophage polarization, increases Runx2 and OSX	Mouse with infectious defect, hDPSCs	Mesoporous silica nanoparticles	Enhances osseointegration in inflammatory environments
(4)	2021	BRD4 in hBMSCs osteogenic differentiation	Unspecified (glucose metabolism miRNAs)	Regulates NF- κ B via Wnt4, increases ALP and Runx2	Human hBMSCs	BRD4 inhibition	Improves osteogenesis in osteoporosis
(8)	2023	IBC in RANKL-induced osteoclastogenesis	miR-193-3p	Inhibits phosphorylation of I κ B α and p65 NF- κ B, reduces c-Fos, NFATc1	Mouse BMMs	Isobavachalcone	Reduces peri-implantitis by inhibiting osteoclasts
(9)	2022	miR-137 in hBMSCs osteogenic differentiation	miR-137	Activates TLR4/NF- κ B via KDM4A, increases p-p65, reduces Runx2	Human hBMSCs	Anti-miR-137	Reverses osteogenesis inhibition in inflammation
(14)	2021	miR-708-5p in SZCs senescence	miR-708-5p	Reduced miR-708-5p activates TLR4/NF- κ B, increases p21 and ROS	Human SZCs, mouse UAC	miR-708-5p mimic	Reduces inflammation in implant loading

Reference Number	Publication Year	Study Title/Summary	Key miRNAs	Main Findings (Related to NF-κB and Inflammation)	Study Model	Type of Therapeutic Intervention	Application in Osseointegration
(20)	2020	miR-100-5p in OVX bone loss	miR-100-5p	Inhibits NF-κB/FGF21, reduces NFATc1, increases Runx2	OVX mouse	miR-100-5p agomir	Reverses bone resorption
(15)	2023	miR-100-5p in OVX-induced bone loss	miR-100-5p	Inhibits NF-κB and FGF21, reduces Ctsk, increases ALP	OVX mouse	miR-100-5p agomir	Improves BMD for implant stability
(7)	2022	Icariin in LPS-induced bone loss	miR-34c	Reduces miR-34c, inhibits NF-κB/IκBα, increases BMP2	Human MSCs	Icariin	Neutralizes LPS-induced inflammation
(19)	2021	Si(OH) ₄ in hMSCs osteogenic differentiation	miR-146a	Increases miR-146a, inhibits NF-κB, increases Col1	hMSCs, MC3T3-E1	Silicon-based biomaterials	Implant coating with reduced inflammation
(13, 16, 21, 45, 46)	2018-2023	miRNA studies in periodontitis, OVX, and osteoclastogenesis	miR-182, miR-139-5p, miR-705, others	Modulates NF-κB via FoxO1, TLR4, RANKL; reduces ROS, increases Runx2/ALP	OVX mouse, pPDLSCs, BMMSCs	Agomir/antagomir, lncRNA-POIR	Enhances osteogenesis and reduces peri-implantitis

The table includes reference numbers, publication years, study summaries, key miRNAs, main findings related to NF-κB and inflammation, study models, therapeutic interventions, and their applications in osseointegration, based on 41 reviewed studies.

For example, miR-146a diminishes osteoclastogenesis and enhances osteogenic markers like Runx2 and OSX by reducing NF-κB through macrophage polarization towards the M2 phenotype (2, 19). Similarly, miR-21a-5p facilitates bone regeneration and angiogenesis in periodontitis models by obstructing the nuclear translocation of p65 NF-κB and the synthesis of iNOS and IL-1β (2). In contrast, miR-137 inhibits osteogenesis via activating TLR4/NF-κB through the targeting of KDM4A, illustrating the opposing roles of miRNAs within this pathway (9). These findings suggest that miRNAs may serve as molecular mechanisms for the precise regulation of inflammation.

The impact of research models on outcomes of the analyzed research, 22 utilized rats (predominantly mice), 13 employed human cell models (including hBMSCs and pPDLSCs), and 6 combined mixed models (Figure 4) (2, 18, 19). Rats, such as OVX mice, have provided substantial insights into the effects of estrogen deficiency on osseointegration. For example, miR-100-5p reduces bone resorption and increases osteogenic markers such as ALP and Runx2 in OVX

models by inhibiting the NF-κB/FGF21 axis (15). Human cell models, including hDPSCs and MC3T3-E1, have demonstrated the role of biomaterials, such as silica nanoparticles (2) and Si(OH)₄ (19), in alleviating inflammation. However, the lack of human clinical studies represents a substantial limitation. The predominant data was obtained from preclinical models, which may not be wholly relevant to human conditions (2, 10, 11, 15, 16, 21).

This underscores the need for clinical research to confirm the results. Therapeutic interventions and clinically feasible approaches utilizing miRNA, such as agomirs, antagomirs, and biomaterials, show strong promise for enhancing osseointegration. Agomir miR-100-5p reduced osteoclastic activity and enhanced bone mineral density (BMD) in OVX models (15). Mesoporous silica nanoparticles (MSNs) encapsulating miR-146a enhance macrophage polarization towards the M2 phenotype and facilitate osteogenesis in inflammatory environments (2). Similarly, silicon biomaterials (Si(OH)₄) inhibit NF-κB and enhance osteogenic markers like Col1 by increasing the expression of miR-146a (19). Natural

compounds such as icariin alleviate LPS-induced inflammation by reducing miR-34c levels and inhibiting NF- κ B/I κ B α phosphorylation, hence facilitating periodontal regeneration (7). These medicines demonstrate potential for managing peri-implantitis and improving implant stability; nevertheless, they require clinical trials to assess safety and efficacy.

Challenges and Constraints of the Research

Despite significant advancements, the recent research still exhibit issues. Most investigations predominantly concentrate on preclinical models, resulting in a dearth of human clinical data (1, 7, 8, 20, 24). This limitation reduces the ability to generalize the results to real patients. Secondly, inconsistencies have been observed in the roles of specific miRNAs (e.g., miR-137 (Yu, 2023 #5) against miR-146a (19)), potentially due to differences in the study model or experimental techniques. Thirdly, the long-term effects of miRNA therapies (such as agomirs and antagomirs) in chronic inflammatory settings are insufficiently investigated (15, 19). The complex interactions between miRNAs and lncRNAs, such as lncRNA-POIR and miR-182 (21), require more examination to elucidate the particular mechanisms involved.

Guidelines for the Future

The findings summarized in this review highlight several priorities for future research. Initially, human clinical trials are essential to validate the effects of miRNAs and biomaterials in patients with periodontitis or osteoporosis. Secondly, the development of enhanced delivery technologies, such as customized nanoparticles, can render miRNA therapies safer and more efficacious (2, 19). Third, investigating the interactions between miRNAs and lncRNAs, such as the lncRNA-POIR/miR-182 axis (21), may offer novel strategies for regulating NF- κ B. Ultimately, computational modeling to predict the aggregate effects of many miRNAs on the NF- κ B pathway can aid in the creation of personalized therapeutics.

This review revealed that the NF- κ B pathway is a crucial regulator of inflammation and osseointegration in dental implants. MicroRNAs, specifically miR-146a, miR-21a-5p, miR-182, and miR-100-5p, attenuate inflammation, reactive oxygen species (47), and osteoclastogenesis by suppressing factors such as FoxO1, TLR4, and FGF21, while concurrently

promoting osteogenic markers like Runx2 and ALP (2, 15, 19, 48). Disruption in these axes leads to peri-implantitis and implant failure, while miRNA-based treatments (such as agomirs, antagomirs, and biomaterials) demonstrate considerable potential for improving osseointegration (19, 20, 32, 48). However, limitations such as the scarcity of human clinical evidence and inconsistencies in the action of certain miRNAs (9, 19) underscore the need for further research. Future research should prioritize clinical research, advanced delivery systems, and miRNA-lncRNA interactions to improve therapeutic efficacy for the successful integration of dental implants. These findings underscore the significance of miRNA in regulating NF- κ B to enhance the longevity of dental implants. They also provide researchers a place to start for their next projects.

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