

Incretin-Based Antidiabetic Therapies and Orthodontic Tooth Movement: Biological Mechanisms, Evidence, and Clinical Implications

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Abstract

Background

The increasing prevalence of type 2 diabetes mellitus and obesity has resulted in a growing number of orthodontic patients receiving incretin-based therapies, particularly glucagon-like peptide-1 receptor agonists (GLP-1RAs) and glucose-dependent insulintropic polypeptide (GIP)-related agents. Beyond glycemic control, these medications regulate bone remodeling, inflammatory signaling, and osteoclast–osteoblast interactions, raising important questions regarding their influence on orthodontic tooth movement (OTM).⁽¹⁻⁴⁾

Objective

To summarize current evidence regarding the effects of incretin-based antidiabetic therapies on bone remodeling during orthodontic tooth movement and discuss their potential clinical implications for orthodontic treatment.

Methods

A comprehensive literature review was conducted using experimental studies, clinical investigations, systematic reviews, and mechanistic reviews evaluating GLP-1 receptor agonists, GIP signaling, bone metabolism, osteoclastogenesis, and orthodontic tooth movement. Evidence was synthesized to describe biological mechanisms, experimental findings, and current clinical relevance.

Results

Available evidence indicates that incretin signaling modulates bone remodeling by suppressing inflammatory cytokines, reducing RANKL-mediated osteoclast differentiation, promoting osteoblast activity, and improving bone quality. Experimental orthodontic studies consistently demonstrate that GLP-1 receptor agonists decrease osteoclastogenesis, reduce alveolar bone resorption, slow orthodontic tooth movement, and diminish orthodontically induced inflammatory root resorption. Similar findings have been reported for GIP signaling, suggesting a regulatory role in force-induced bone remodeling. However, nearly all orthodontic evidence originates from animal models, while clinical studies in orthodontic patients remain unavailable.⁽²⁻⁸⁾

Conclusions

Incretin-based therapies appear to influence orthodontic tooth movement through modulation of bone remodeling and inflammatory pathways. Although current preclinical evidence suggests reduced tooth movement and potential protection against root resorption, the absence of prospective human studies limits clinical translation. Well-designed clinical investigations are required before orthodontic treatment protocols can be modified for patients receiving these medications.⁽⁵⁻⁸⁾

Keywords: Orthodontic tooth movement; GLP-1 receptor agonists; glucose-dependent insulintropic polypeptide; incretin therapy; bone remodeling; osteoclastogenesis; diabetes mellitus; root resorption.

1. Introduction

The increasing prevalence of type 2 diabetes mellitus (T2DM) and obesity has substantially increased the number of adults seeking orthodontic treatment while receiving long-term pharmacological therapy. Among the most significant therapeutic advances in metabolic disease management are incretin-based antidiabetic agents, particularly glucagon-like peptide-1 receptor agonists (GLP-1RAs) and the newer glucose-dependent insulintropic polypeptide (GIP)-based therapies.⁽¹⁻⁴⁾ Initially developed to improve glycaemic control through glucose-dependent insulin secretion, these agents have demonstrated additional cardiovascular, renal, anti-inflammatory, and weight-reducing benefits, leading to their widespread clinical use^(1-2,9). Emerging evidence further suggests that incretin signaling extends beyond glucose homeostasis to influence bone remodeling, skeletal metabolism, and immune regulation, thereby introducing important considerations for orthodontic practice^(2-4,9).

Orthodontic tooth movement (OTM) is a biologically regulated process initiated by the application of mechanical forces to teeth, resulting in remodeling of the periodontal ligament and surrounding alveolar bone. This process depends on a tightly coordinated balance between osteoclast-mediated bone resorption on the compression side

and osteoblast-mediated bone formation on the tension side. Cellular and molecular mediators, including receptor activator of nuclear factor- κ B ligand (RANKL), osteoprotegerin (OPG), tumor necrosis factor- α (TNF- α), interleukins, and prostaglandins, regulate these events and ultimately determine the rate and quality of tooth movement⁽¹⁰⁻¹¹⁾. Consequently, systemic diseases and medications capable of modifying inflammatory responses or bone metabolism may significantly influence orthodontic treatment duration, periodontal remodeling, and the development of adverse effects such as orthodontically induced inflammatory root resorption (OIIRR)⁽¹⁰⁻¹²⁾.

Recent experimental studies have identified incretin signaling as an important regulator of the gut–bone axis. GLP-1 receptor agonists and GIP-related therapies have been shown to suppress osteoclast differentiation, reduce inflammatory cytokine production, promote osteoblast activity, and improve bone quality through modulation of the RANKL/OPG signaling pathway⁽²⁻⁴⁾. Animal models have consistently demonstrated that activation of GLP-1 and GIP signaling reduces orthodontic tooth movement⁽⁵⁻⁸⁾, decreases osteoclast numbers, and limits root resorption, whereas disruption of incretin signaling accelerates alveolar bone remodeling and tooth movement. In parallel, systematic reviews have reported favorable effects of GLP-1RAs on bone turnover markers and bone mineral density, supporting their broader skeletal actions beyond glycaemic regulation⁽²⁾.

Despite these promising findings, current evidence remains predominantly derived from animal experiments and mechanistic studies, with limited information regarding the clinical implications of incretin-based therapies during orthodontic treatment in humans^(5-8,12). As the number of orthodontic patients receiving these medications continues to increase, clinicians require a comprehensive understanding of their potential effects on alveolar bone remodeling and treatment outcomes. Therefore, this review synthesizes the current evidence on the biological mechanisms through which incretin-based antidiabetic therapies influence bone remodeling and orthodontic tooth movement and discusses their potential clinical implications while highlighting existing knowledge gaps and priorities for future research.

2.1 Incretin Signaling and Bone Remodeling

Bone remodeling is a continuous process regulated by the coordinated activities of osteoclasts and osteoblasts. During orthodontic tooth movement (OTM), mechanical forces induce localized inflammatory responses that activate the receptor activator of nuclear factor- κ B ligand (RANKL)/osteoprotegerin (OPG) signaling pathway, which governs osteoclast differentiation and alveolar bone resorption. Pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , and IL-6, further regulate bone turnover and influence the rate of tooth movement^(10,11).

Incretin hormones, particularly glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), contribute to bone remodeling through the gut–bone axis^(3,9). Experimental studies demonstrate that GLP-1 receptor agonists suppress inflammatory cytokines, reduce RANKL expression, inhibit osteoclastogenesis, and promote osteoblast activity, thereby shifting bone remodeling toward bone preservation^(2-4,6-9). Similarly, GIP signaling enhances osteoblast function while limiting osteoclast-mediated bone resorption, improving bone quality and mineral density.^(3,7,8,9) These biological effects suggest that incretin-based therapies can influence alveolar bone remodeling and may alter the rate of orthodontic tooth movement in patients receiving these medications. (Fig 1) (Table1)

Figure 1. Proposed mechanisms by which incretin-based therapies regulate alveolar bone remodeling during orthodontic tooth movement.

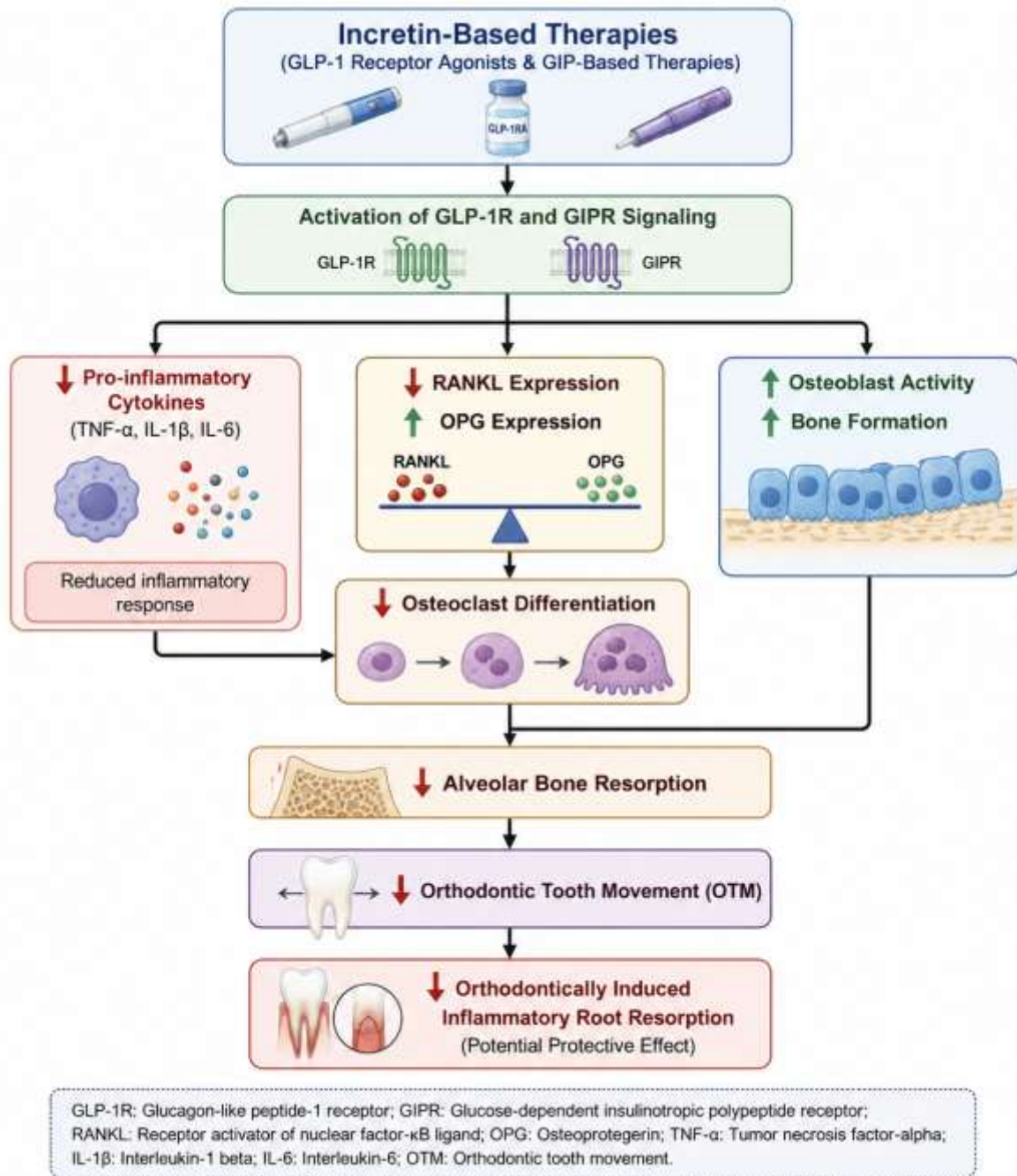


Figure 1. Proposed mechanisms by which incretin-based therapies regulate alveolar bone remodeling during orthodontic tooth movement. The schematic summarizes the reported effects of GLP-1 receptor agonists and GIP signaling on inflammatory cytokines, the RANKL/OPG pathway, osteoclastogenesis, osteoblast activity, alveolar bone remodeling, orthodontic tooth movement, and root resorption. Adapted from references ^[4-8]

Table 1. Biological effects of incretin-based therapies on bone remodeling and their orthodontic relevance

Biological Target/Pathway	Effect of Incretin-Based Therapies	Potential Orthodontic Relevance
Pro-inflammatory cytokines (TNF-α, IL-1β, IL-6)	Decreased expression of inflammatory mediators	Reduced inflammatory response and osteoclast activation

RANKL/OPG signaling	↓ RANKL expression, ↑ OPG expression, resulting in a reduced RANKL/OPG ratio	Inhibition of osteoclast differentiation and activity
Osteoclastogenesis	Suppression of osteoclast formation and bone-resorptive function	Reduced alveolar bone resorption and slower orthodontic tooth movement
Osteoblast activity	Enhanced osteoblast differentiation and bone formation	Improved bone quality and maintenance of alveolar bone
Bone remodeling	Shift toward bone preservation with reduced bone turnover	Altered rate of orthodontic tooth movement
Root resorption	Decreased odontoclast activity and inflammatory root resorption	Potential protection against orthodontically induced inflammatory root resorption (OIIRR)

(**Abbreviations:** IL, interleukin; OPG, osteoprotegerin; OIIRR, orthodontically induced inflammatory root resorption; RANKL, receptor activator of nuclear factor- κ B ligand; TNF- α , tumor necrosis factor- α .)

Source: Compiled from references [2-4,6-9]

2.2 Effects of Incretin-Based Therapies on Orthodontic Tooth Movement

Current evidence regarding the effects of incretin-based therapies on orthodontic tooth movement (OTM) is derived primarily from animal studies.⁽⁵⁻⁸⁾ Experimental models consistently demonstrate that GLP-1 receptor agonists, particularly exendin-4, reduce the rate of OTM by suppressing osteoclast differentiation and alveolar bone resorption⁽⁵⁻⁶⁾. Local administration of exendin-4 significantly decreased tooth movement, osteoclast and odontoclast numbers, root resorption, and the expression of RANKL and TNF- α , while reducing the RANKL/OPG ratio without affecting OPG expression⁽⁵⁻⁶⁾.

Similarly, studies evaluating GIP signaling reported that activation of GIP receptors inhibited osteoclastogenesis and reduced orthodontic tooth movement, whereas GIP receptor deficiency accelerated alveolar bone remodeling and increased tooth movement.⁽⁷⁻⁸⁾ More recently, the DPP-4-resistant GIP analogue (D-Ala²)GIP demonstrated inhibitory effects on TNF- α -induced osteoclast formation, bone resorption, and root resorption during orthodontic treatment. Collectively, these findings suggest that incretin-based therapies modulate bone remodeling by suppressing inflammatory and osteoclastic activity, potentially prolonging orthodontic treatment while providing protection against orthodontically induced inflammatory root resorption⁽⁵⁻⁸⁾. However, these observations are currently limited to preclinical studies, and human clinical evidence remains unavailable^(10,11). (Table 2)

Table 2. Summary of Experimental Studies Evaluating Incretin-Based Therapies and Orthodontic Tooth Movement

Study	Study Design / Model	Intervention	Major Findings	Orthodontic Relevance
Shen et al., 2021	Mouse model of orthodontic tooth movement	Local exendin-4 (GLP-1RA) administration	Reduced orthodontic tooth movement, osteoclast and odontoclast numbers, RANKL and TNF- α expression, and root resorption	GLP-1RAs suppress osteoclastogenesis and protect against OIIRR
Yamauchi et al., 2022	GIP receptor knockout mice	GIP receptor deficiency	Accelerated tooth movement, increased osteoclast activity, and greater alveolar bone loss	Endogenous GIP signaling regulates force-induced bone remodeling
Lin et al., 2025	Mouse model of orthodontic tooth movement	(D-Ala ²)GIP analogue	Inhibited TNF- α -induced osteoclastogenesis, reduced bone resorption, tooth movement, and root resorption	GIP analogue exhibits osteoprotective effects during OTM
Li et al., 2024	Systematic review and	GLP-1 receptor agonists	Increased bone mineral density, increased osteocalcin	Supports favorable effects of GLP-1RAs on skeletal metabolism

	meta-analysis (26 RCTs)		and bone alkaline phosphatase, reduced CTX	
Kitaura et al., 2021	Narrative review	GLP-1RAs and DPP-4 inhibitors	Enhanced osteoblast activity and suppressed osteoclast differentiation through anti-inflammatory pathways	Biological rationale for altered orthodontic bone remodeling
Zhao et al., 2024	Mechanistic review	GLP-1, GIP and GLP-2 signaling	Demonstrated the role of incretins in regulating the gut–bone axis, bone formation, and bone resorption	Supports the mechanistic basis for the influence of incretin signaling on orthodontic bone remodeling

(Abbreviations: CTX, C-terminal telopeptide of type I collagen; GIP, glucose-dependent insulintropic polypeptide; GLP-1RA, glucagon-like peptide-1 receptor agonist; OIIRR, orthodontically induced inflammatory root resorption; OTM, orthodontic tooth movement; RANKL, receptor activator of nuclear factor- κ B ligand; TNF- α , tumor necrosis factor- α .)

Source: Data summarized from references ^[2–5,7,8]

3. Clinical Implications for Orthodontic Practice

The increasing use of GLP-1 receptor agonists and GIP-based therapies among adults with type 2 diabetes and obesity has important implications for orthodontic care^(1,3,9). Experimental evidence suggests that these agents suppress osteoclast activity and reduce alveolar bone remodeling, potentially slowing orthodontic tooth movement and extending treatment duration^(5–8). At the same time, their anti-inflammatory and osteoprotective effects may reduce the risk of orthodontically induced inflammatory root resorption and help preserve alveolar bone integrity^(5–8).

Orthodontists should obtain a comprehensive medical history, including the use of incretin-based medications, before initiating treatment^(10,11). Although current evidence does not justify altering treatment protocols solely on the basis of these therapies, clinicians should recognize the possibility of altered biological responses, particularly in patients receiving long-term GLP-1RAs or dual incretin agonists^(1,10,11). As existing evidence is derived almost exclusively from animal studies, prospective human studies are required to determine their clinical impact on treatment efficiency, force application, and long-term outcomes before definitive clinical recommendations can be established^(5,8,10,11).

4. Future Directions and Conclusion

Despite growing evidence supporting the role of incretin signaling in bone remodeling, its implications for orthodontic treatment remain incompletely understood^(2,4). Current knowledge is based predominantly on animal models and experimental studies, with a lack of prospective clinical trials evaluating the effects of GLP-1 receptor agonists and GIP-related therapies on orthodontic tooth movement in humans^(5–8,10,11). Future research should focus on longitudinal clinical studies to determine treatment duration, optimal force application, periodontal outcomes, and the incidence of orthodontically induced inflammatory root resorption in patients receiving these medications^(10,11). Additionally, investigations into dose-dependent effects and newer dual incretin agonists may further clarify their role in orthodontic practice^(3,8,9).

Incretin-based antidiabetic therapies represent promising modulators of alveolar bone remodeling through their anti-inflammatory and osteoprotective actions^(2–4,9). Experimental evidence suggests that these agents suppress osteoclastogenesis, reduce orthodontic tooth movement, and limit root resorption by regulating the RANKL/OPG pathway and inflammatory cytokines^(5–8). Although these findings indicate potential implications for orthodontic treatment planning, translation into routine clinical practice requires robust human evidence^(10,11). Until such data become available, orthodontists should recognize the possible influence of incretin-based therapies while managing patients receiving these medications. (Table 3)

Table 3. Clinical Implications of Incretin-Based Therapies for Orthodontic Practice

Clinical Consideration	Potential Implication	Current Evidence
Orthodontic tooth movement	May reduce the rate of tooth movement due to suppression of osteoclast activity	Supported by animal studies; no human clinical evidence
Treatment duration	Orthodontic treatment may be prolonged	Hypothesized; requires prospective clinical studies
Orthodontically induced inflammatory root resorption (OIIRR)	May decrease root resorption by reducing osteoclast and odontoclast activity	Supported by preclinical studies
Alveolar bone remodeling	Reduced bone resorption with preservation of bone quality	Supported by mechanistic and experimental evidence
Treatment planning	Obtain a detailed medical history, including GLP-1RA/GIP therapy	Recommended for all adult orthodontic patients
Force application	No evidence currently supports modification of orthodontic force magnitude	Clinical protocols should remain unchanged until human evidence is available
Future perspectives	Prospective clinical trials are needed to evaluate treatment outcomes in patients receiving incretin-based therapies	High research priority

(**Abbreviations:** GIP, glucose-dependent insulintropic polypeptide; GLP-1RA, glucagon-like peptide-1 receptor agonist; OIIRR, orthodontically induced inflammatory root resorption.)

Source: Compiled from references [1–8,10–12].

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