Biological mechanism of surgery-mediated acceleration of orthodontic tooth movement: A narrative review

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Abstract
Surgery-mediated acceleration of orthodontic tooth movement (SAOTM) has been proven effective for decades. Research has confirmed that surgical approaches play an important role in adult patients with a short orthodontic treatment time. The mechanism of SAOTM involves short-term acceleration of localized hard and soft tissue remodeling, known as the regional acceleratory phenomenon. However, no relevant review on the biological mechanism of SAOTM has been performed to date. The proposed biological mechanism of acceleration of OTM involves the participation of various cells, cytokines, and signaling pathways. We herein review the relevant literature and summarize the biological mechanism of SAOTM to provide new insights for further research on acceleration of OTM.

Keywords
Surgery, orthodontic tooth movement, regional acceleratory phenomenon, biological mechanism, cell, cytokine, signaling pathway

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Introduction
Adult orthodontic patients usually pay more attention to orthodontic efficiency than do younger patients because of consideration regarding aesthetics and convenience. However, they tend to have longer orthodontic treatment time than adolescent
patients because of their lower bone metabolic rate and the need for a more complicated interdisciplinary treatment plan.\textsuperscript{1} Prolonged orthodontic treatment has many disadvantages, such as oral hygiene-related problems, gingival recession, and root resorption.\textsuperscript{2–4} Therefore, many researchers have focused on new approaches to accelerate orthodontic tooth movement (OTM).

Studies have shown that acceleration of OTM can be achieved by surgical, nonsurgical, and biological approaches (Table 1).\textsuperscript{5–7} Of these methods, surgery-mediated acceleration of OTM (SAOTM) has the most predictable outcomes.\textsuperscript{7} Although some surgical approaches have not been popularized because of their high invasiveness, the effectiveness of SAOTM has been reported in many cases of interdisciplinary treatment.\textsuperscript{8,9} Currently, there is a consensus that the cause of SAOTM is the regional acceleratory phenomenon (RAP) rather than bone block movement.\textsuperscript{10,11} However, the specific cellular and molecular mechanisms underlying the RAP remain unclear. Therefore, this review focuses on the biological mechanism of SAOTM from four aspects: the mechanism of OTM, the RAP in SAOTM, the commonly used approaches of SAOTM, and the biological response in SAOTM.

**Literature search**

We performed a systematic search of PubMed, Embase, the Cochrane Library, and the Web of Science supplemented by a manual search. The search was limited to the publication years of January 2012 to March 2022 and used a combination of the following keywords: “corticotomy” OR “periodontally accelerated osteogenic orthodontics” OR “piezocision” OR “micro-osteoperforations” AND “orthodontics.” Expanded keywords and the abbreviations “PAOO” (periodontally accelerated osteogenic orthodontics), “MOP” (micro-osteoperforation), and “OTM” also received attention. The inclusion criteria were articles, reviews, and systematic reviews related to the biological mechanism of OTM and SAOTM. The exclusion criteria were non-English articles, case reports, editorials, comments, conference abstracts, research letters, and studies that did not involve cells, cytokines, or signaling pathways (Figure 1).

| Surgical approaches                          | Nonsurgical approaches                        | Biological approaches                         |
|---------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Interseptal bone reduction                  | Resonance vibration                           | Interleukins (IL-1, IL-2, IL-6, and IL-8)     |
| Distraction osteogenesis                    | Electrical current                            | Macrophage colony-stimulating factor          |
| Alveolar osteotomy-assisted tooth movement  | Static magnetic field                         | Receptor activator of nuclear factor-κB ligand (RANKL) |
| Alveolar corticotomy-assisted tooth movement| Pulsed electromagnetic field                  | Tumor necrosis factor-α                       |
| Periodontally accelerated osteogenic orthodontics | Cyclical force                             | Prostaglandin E2                               |
| Piezocision                                 | Low-intensity laser therapy                   | Epidermal growth factor                       |
| Micro-osteoperforation                      | Low-level light therapy                       | Parathyroid hormone                           |
| Orthognathic “surgery-first” orthodontic treatment |                                      | L-thyroxine                                   |
|                                            |                                               | 1,25-dihydroxyvitamin D3                      |
|                                            |                                               | Relaxin                                       |

Table 1. Approaches to acceleration of orthodontic tooth movement.
Mechanism of OTM

The mechanism of OTM is based on the response of the periodontal ligament (PDL) and alveolar bone to mechanical stimulation. The alveolar bone modeling and remodeling process is accompanied by bone formation on the tension side and bone resorption on the compressed side. This process consists of three phases of OTM: the initial phase (rapid movement after force is applied), the lag phase (little or no movement), and the final phase (gradual or sudden increase in movement). The responses of cells, cytokines, and signaling pathways play an important role in these processes. The rate of these processes is determined by the activity level of bone cells (osteoclasts, osteoblasts, and osteocytes), which are under control of mechanical and biochemical factors. Therefore, the quantity and quality of OTM can be controlled by interfering with the underlying mechanism and biological pathways.

Surgery-induced RAP

During orthopedic surgery, a transient burst of localized bone remodeling occurs.
at the site of surgical injury to the cortical bone.\textsuperscript{17} This response is described as the RAP because it causes a local decrease in bone density while accelerating the healing phase.\textsuperscript{10,11} Before the introduction of the RAP into SAOTM, it was believed that osteotomy-assisted acceleration of OTM was caused by bone block movement.\textsuperscript{18}

The mechanism of SAOTM is currently believed to be the surgery-induced RAP, which is a process of increased demineralization–mineralization around the surgical area.\textsuperscript{19,20} Because the RAP is a brief burst of healing, the early postoperative period needs to be fully utilized during OTM. The effects of the RAP begin a few days after surgery and peak within 1 to 2 months. This effect usually lasts for 4 months but may take 6 to 24 months to completely subside.\textsuperscript{10} Therefore, it is necessary to take advantage of the initial window of rapid tooth movement.\textsuperscript{21} However, the specific cellular and molecular mechanisms involved in SAOTM remain largely unknown.\textsuperscript{22} Therefore, reviewing the biological mechanism of SAOTM is expected to provide new strategies for accelerating OTM.

**Approaches and mechanisms of SAOTM**

There are many approaches of SAOTM, including interseptal bone reduction, distraction osteogenesis, alveolar osteotomy,
alveolar corticotomy, periodontally accelerated osteogenic orthodontics (PAOO), piezocision, micro-osteoperforation (MOP), and orthognathic “surgery-first” orthodontic treatment. However, some of these surgical approaches never gained popularity because of their apparent invasiveness. Among the many available surgical approaches, corticotomy, PAOO, piezocision, and MOP are less invasive and therefore widely used.

Alveolar osteotomy- and corticotomy-assisted tooth movement

Osteotomy refers to the simultaneous surgical cutting of cortical and medullary bone, whereas corticotomy refers to the cutting or perforation of only the cortical bone while leaving the medullary bone unchanged. The mechanism of osteotomy was once thought to be the movement of the bone block as a unit, and the mechanism of corticotomy was thought to be a reduction in the resistance of cortical bone.23,24 However, osteotomy is no longer widely used because of its high invasiveness.

A previous theory suggested that cortical bone is a major barrier to OTM.18 However, computed tomography evaluations of patients undergoing corticotomy showed that rapid tooth movement was not due to reduced cortical resistance but was consistent with the wound healing pattern of the RAP.19 Therefore, the approach of SAOTM requires surgery involving only the cortical layer to induce the RAP. An understanding of the biological mechanism of SAOTM allows continuous improvement of surgical approaches to reduce invasiveness. This has increased the acceptance of SAOTM in clinical practice.

PAOO

PAOO is a procedure that combines selective alveolar corticotomy with granular bone grafting.19 Granular bone grafting can enhance local bone volumes, while selective alveolar corticotomy can accelerate OTM based on the RAP.25 This is especially important in adults because their bone regeneration capacity is much lower than that in children. In addition, for orthodontic patients with interdisciplinary treatment needs, PAOO can not only combine tissue engineering principles with periodontal regenerative surgery but also achieve rapid OTM.26

Piezocision

To induce the RAP, the surgeon must cut into the cortical layer. Therefore, most surgical procedures involve dissection of a mucoperiosteal flap. However, this increases the risk of discomfort and postoperative pain. With this consideration, a surgical approach that combines limited invasiveness, improved precision, and treatment of periodontal problems is proposed. In the piezocision technique, a primary incision is made on the buccal gingiva first, and then the buccal cortex is incised with a Piezo surgical knife.27 Research shows that this technique can effectively accelerate OTM without significant periodontal damage.28

MOP

MOP is another technique that reduces the invasiveness of surgery while still being effective in eliciting the RAP. This technique further reduces soft tissue damage by perforating the cortical bone through the mucosa using a Propel device (Propel Orthodontics, Briarcliff Manor, NY, USA).29 Studies have shown that MOP significantly increases the expression of cytokines, thereby accelerating OTM.30,31

Biological responses of SAOTM

The biological mechanism of SAOTM is mainly enhancement of local bone
metabolism through the RAP with resultant acceleration of local bone remodeling. This involves the participation of cells as well as cytokines and signaling pathways (Figure 3).

**Macrophages**

Macrophages play an important role in bone wound healing. Their main functions include mediation of inflammation by the M1 subtype and mediation of regeneration by the M2 subtype. Studies have shown that macrophages are not only involved in the regulation of bone tissue homeostasis during bone injury but also in the resorption of alveolar bone on the compressed side during OTM-induced alveolar bone remodeling. Furthermore, the amount of corticotomy-assisted OTM is significantly reduced when macrophages are decreased in mice. These findings suggest that macrophages play an important role in the biological response of SAOTM.

SAOTM induces local osteoclastogenesis and macrophage infiltration, a process mediated by tumor necrosis factor (TNF)-α. Subsequently, surgical stimulation immediately polarizes macrophages to an M1-like phenotype by activating the NF-κB signaling pathway, and the macrophages then switch to an M2-like

![Figure 3. Cells, cytokines, and signaling pathways involved in surgery-mediated acceleration of orthodontic tooth movement.](image-url)
phenotype by activation of the JAK/STAT3 signaling pathway.\textsuperscript{22} Therefore, considering that macrophages are closely involved in SAOTM, regulating macrophages might be an effective way to accelerate OTM.

**Osteoclasts**

OTM is dependent on osteoclast-induced bone resorption on the compressed side of the alveolar bone.\textsuperscript{39} One study showed that compared with OTM alone, corticotomy-assisted OTM increased the number of osteoclasts, especially at week 2 after surgery.\textsuperscript{22} Another study produced the same result at week 2 after corticotomy-assisted OTM, whereas at week 4, the number of osteoclasts was not significantly different between corticotomy-assisted OTM and OTM alone.\textsuperscript{40} In another SAOTM approach, MOP-assisted OTM resulted in significantly more osteoclasts on the compressed side of the alveolar bone at day 12 compared with OTM alone.\textsuperscript{37} Furthermore, MOP-assisted OTM with a higher number of perforations increased the amount of osteoclast-induced bone resorption on the compressed side of the alveolar bone, which in turn increased alveolar bone remodeling.\textsuperscript{41} In summary, the number of osteoclasts is strongly associated with SAOTM. Accordingly, regulating osteoclast-related cytokines might be another strategy to accelerate OTM.

Osteoclasts are derived from hematopoietic stem cells, and their differentiation process includes four phases.\textsuperscript{42,43} Colony-forming unit–monocytes reside in the bone marrow and can further transform into monoblasts, which in turn give rise to monocytes. After monocytes are released into the blood, they migrate to bone tissue and differentiate into mononuclear osteoclasts, which eventually fuse to form multinuclear osteoclasts. Two essential factors are involved in the process of osteoclastogenesis: macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor κB ligand (RANKL).\textsuperscript{44,45} Therefore, by regulating the expression of M-CSF and RANKL, the proliferation and differentiation of osteoclasts can be regulated. The proinflammatory cytokine TNF-\(\alpha\) also plays an important role in the induction of osteoclast differentiation.\textsuperscript{46,47}

**M-CSF.** M-CSF is mainly present in osteoblasts and fibroblasts.\textsuperscript{44} It affects the formation and activation of osteoclasts by stimulating osteoclast proliferation and differentiation and inhibiting osteoclast apoptosis.\textsuperscript{42,48} Studies have shown that in corticotomy-assisted OTM, the expression of M-CSF in the alveolar bone around the OTM teeth is significantly increased at day 3 and further increased at week 2.\textsuperscript{48,49} The increase in M-CSF suggests that SAOTM leads to increased proliferation and differentiation of osteoclasts.\textsuperscript{49} In the signaling pathway involved in this process, M-CSF triggers its receptor M-CSFR and subsequently induces the mitogen-activated protein kinase (MAPK) phosphorylation cascade.\textsuperscript{50} Thus, increasing the expression of M-CSF to activate the MAPK signaling pathway might be a potential way to regulate osteoclasts in the acceleration of OTM.

**RANKL/RANK/OPG.** Three core molecules are involved in osteoimmunity: RANKL, RANK, and osteoprotegerin (OPG). RANKL, a member of the TNF superfamily, promotes osteoclast differentiation by recognizing its receptor RANK, which is expressed on the surface of osteoclast precursors.\textsuperscript{45} OPG is a member of the TNF receptor superfamily and acts as a decoy receptor for RANKL, which inhibits osteoclast differentiation.\textsuperscript{51} Therefore, an increase in RANKL expression without a change in OPG suggests that osteoclasts are triggering bone resorption.
In one study, the expression of RANKL in corticotomy-assisted OTM steadily increased from week 1 to week 3, whereas its expression in OTM alone increased only at week 1 and then gradually decreased from week 2. Another SAOTM approach, selective alveolar decortication-facilitated OTM, produced the same result. RANKL-induced osteoclast differentiation involves signal pathways including TNF receptor-associated factor 6 (TRAF6, the most important factor in osteoclast differentiation), c-Jun N-terminal kinase (JNK, one of the three main subfamilies of MAPKs, activated by TRAF6), c-Jun (an important transcription factor that promotes osteoclast formation, activated by JNK), and nuclear factor of activated T cells 1 (NFATc1, involved in maintaining osteoclast lineage commitment, regulated by c-Jun). Research has shown that a mechanism similar to SAOTM can be achieved by stimulating JNK activation and NFATc1 expression during osteoclast differentiation by 6-shogaol. Consequently, activation of any node in the RANKL/RANK signaling pathway may accelerate bone resorption.

One study showed that OPG expression peaked at week 2 in corticotomy-assisted OTM but remained at a low level in the early stage in OTM alone. The same result was obtained in another SAOTM approach: selective alveolar decortication-facilitated OTM. This indicates that SAOTM has a unique biological response to tooth movement; i.e., RANKL coupled with OPG accelerates alveolar bone remodeling. This differs from increased RANKL expression and decreased OPG expression in the traditional OTM-alone pattern.

TNF-α. TNF-α plays an important role on the compressed side of alveolar bone in OTM because it induces osteoclast differentiation, leading to bone resorption. In one study of MOP-assisted OTM, TNF-α expression was increased in the compressed side of the PDL from day 1 to day 10. Another study of MOP-assisted OTM showed that the expression level of TNF-α increased in rat PDL cells. Moreover, in a clinical study, MOP-assisted OTM increased TNF-α expression in human gingival crevicular fluid. However, deficiency of TNF-α slows down OTM in animal experiments. Furthermore, knockout of the TNF receptor in mice significantly shortened the distance of tooth movement in both MOP-assisted OTM and OTM alone and had a greater effect on SAOTM. Considering that increasing TNF-α expression is one of the biological mechanisms of SAOTM, up-regulation of TNF-α expression may be an effective strategy to accelerate OTM.

**Osteoblasts**

OTM also requires osteoblasts to proliferate and mineralize on the tension side of the alveolar bone. The bone remodeling process can be evaluated by the anabolic activity of osteoblast markers such as osteopontin (OPN), bone sialoprotein (BSP), and osteocalcin (OCN). In addition, transforming growth factor (TGF)-β1 and the Wnt signaling pathway, which regulate the proliferation and differentiation of osteoblasts, are also involved in SAOTM.

**OPN.** OPN is a sialic acid-rich secreted phosphoprotein and the major component of the extracellular matrix in mineralized tissues such as bone and cementum. One study showed that in corticotomy-assisted OTM, OPN was abundantly expressed at both week 1 and week 2, whereas in OTM alone, its expression was initially low and gradually increased. This suggests that osteoblasts in SAOTM are more active at an early stage and last longer. Another study produced similar results while also showing that increased osteoclast activity...
in SAOTM was accompanied by higher osteoblastic activity.49

**BSP.** BSP is a noncollagenous matrix protein that plays an important role in hydroxyapatite nucleation at the mineralization front of bone and is positively correlated with osteoblast maturation.61 In corticotomy-assisted OTM, the expression of BSP was significantly increased at week 2, whereas in OTM alone, it was abundantly expressed at week 3.48 This indicates that SAOTM can stimulate osteoblast maturation at an early stage. Similar conclusions were drawn in a study of selective alveolar decortication-facilitated OTM.49 Another study on MOP-assisted OTM showed that BSP expression was enhanced in the cementum region after MOP operations.41 The combined findings of BSP and OPN expression show that bone turnover remains steady in SAOTM.

**OCN.** OCN is a noncollagenous protein secreted by osteoblasts and serves as a marker of osteoblast maturation, reflecting alveolar bone anabolic activity.61 One study showed that in corticotomy-assisted OTM, the expression of OCN peaked at week 2, indicating that alveolar bone remodeling was ongoing.48 Another study showed that the expression of OCN was higher at weeks 1 to 3 in corticotomy-assisted OTM than in OTM alone.41 The above data indicate that SAOTM can regulate the state of bone metabolism at an early stage, resulting in increased osteoblast activity, which in turn accelerates alveolar bone remodeling.

**TGF-β1.** TGF-β1 is a multipotent cellular peptide secreted by a variety of cells, including osteoblasts, fibroblasts, and macrophages. It is widely present in bone and plays an important role in local bone metabolism and bone remodeling.62 TGF-β1 has chemotactic effects on osteoblasts and promotes their proliferation and differentiation, and it inhibits osteoclastogenesis by reducing RANKL and increasing OPG expression.63 TGF-β1 expression appeared earlier on the alveolar bone surface in corticotomy-assisted OTM than in OTM alone.62 This indicates that in SAOTM, TGF-β1 is involved in compensatory remodeling of the alveolar bone surface. Accordingly, increasing the expression of TGF-β1 can promote the remodeling of alveolar bone, which might be another effective strategy to accelerate OTM.

**Wnt.** The importance of Wnt/β-catenin signaling mediated by β-catenin in bone formation has been well verified.64 β-catenin can guide osteoblast progenitors to differentiate into immature osteoblasts.65 In OTM, Wnt/β-catenin in PDL cells induces cementoblast differentiation and regulates cementum formation and mineralization.66 MOP-assisted OTM upregulates Wnt/β-catenin in PDL cells and promotes stronger signaling expression compared with OTM alone.41 Axin2 is a regulator of the classic Wnt signaling pathway, and its expression can reflect the activation level of the Wnt signaling pathway.67 One study showed that the expression level of Axin2 is significantly increased in corticotomy-assisted OTM, confirming that SAOTM stimulates osteogenesis and inhibits root resorption by upregulating the Wnt signaling pathway in PDL.68 One study involving analysis of the PDL around the molar roots showed that MOP-assisted OTM significantly increased the levels of Wnt-responsive Axin2.41 Thus, activation of the Wnt signaling pathway might be an effective strategy to accelerate OTM.

**Conclusion**

Although SAOTM is invasive, it is the most reliable way to accelerate OTM. The biological mechanism of SAOTM was confirmed to be the RAP rather than bone
block movement. Changes in our understanding of the biological mechanism of SAOTM have led to gradual improvements in surgical approaches. The invasiveness of the procedure has gradually decreased, thereby increasing its acceptance in clinical practice.

This review will help to provide new insights for accelerating OTM by positively regulating cells (such as macrophages, osteoclasts, and osteoblasts), cytokines (such as M-CSF, RANKL, TNF-α, and TGF-β1), and signaling pathways (such as NF-κB, JAK/STAT3, MAPK, RANKL/RANK/OPG, and Wnt). Notably, SAOTM exhibits a unique biological mechanism involving the RANKL/RANK/OPG signaling pathway: RANKL coupled with OPG promotes alveolar bone remodeling and accelerates OTM. However, the biological mechanism of SAOTM still needs further study, and we hope that this review will be helpful in promoting such research.

Author contributions
Yun Hu and Hegang Li determined the theme of this review, conducted the literature search, reviewed the literature, and selected the relevant literature. Yun Hu drafted the manuscript. Hegang Li reviewed and critically revised the manuscript.

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The authors declare that there is no conflict of interest.

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Ethics
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