



CIRCADIAN BIOLOGY IN ORTHODONTICS: A NOVEL PERSPECTIVE IN TOOTH MOVEMENT AND TREATMENT OPTIMIZATION

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Abstract : Orthodontic tooth movement (OTM) results from the remodeling of alveolar bone in response to controlled mechanical forces. While traditional studies have examined cellular and molecular mechanisms underlying OTM, recent advances highlight the role of circadian biology in regulating bone metabolism, inflammatory processes, and pain perception. Circadian rhythms, governed by endogenous molecular clocks, orchestrate systemic and local physiological functions including osteoblast and osteoclast activity, hormonal secretion, and immune response. This review synthesizes current knowledge on circadian regulation of bone biology and explores its potential implications in orthodontics. Special emphasis is placed on the timing of force application, drug administration, and patient-centered chronotherapy. Integration of circadian science into orthodontic practice may open new pathways for individualized and biologically synchronized treatment strategies, ultimately improving efficiency and patient outcomes.

Keywords: Circadian rhythm, orthodontics, chronotherapy, orthodontic tooth movement, bone remodeling, orthodontic pain.

INTRODUCTION

Orthodontic tooth movement (OTM) - the bioinductive process of biologically-dependent movement of a tooth - relies on the remodeling of the alveolar bone, stimulated by regulated mechanical stresses. As a result of the orthodontic force, the PDL is tensed. This initiates a cellular-molecular cascade characterized by osteoblast mediated bone apposition on the tension side and osteoclast mediated bone resorption on the pressure side. This dynamic equilibrium enables regulated tooth movement, and also exhibits periodontal health. OTM is affected by the size, direction, and duration of force application, and other, systemic factors, such as hormones, drugs and systemic nutritional state, and patient factors such as age and craniofacial growth pattern. (Krishnan and Davidovitch, 2006).

Recently, circadian biology as a novel modulator of the skeletal physiology has gained consideration. Internal oscillations which coincide with the 24 hour period of day and night receive the name circadian rhythms and they run many biological activities including immune response, hormonal generation metabolism. (Takeda and Maemura, 2016). Studies on bone have demonstrated that bone re-modeling is under the control of the circadian rhythm evidenced by the rhythmic expression of RANKL, OPG and osteocalcin, factors that modulate the activity of osteoblast and osteoclasts. (Fujihara et al., 2018). These results indicate that the responsiveness of bone to mechanical strain and remodeling signals is dependent on time of the day.

Although there is mounting evidence that the biology of bone is related to the circadian rhythm, research of orthodontics in this area in rudimentary has been made. Current treatment regimens do not adequately account for when force is applied, appliances are

activated, or medication is administered. However, as observed in other medical fields, circadian-timed treatment (i.e., chronotherapy), delivers superior efficacy and may reduce toxicities. The concept of chrono-orthodontics, ie, where the concept is translated into orthodontics, assumes that organizing orthodontic treatments according to the natural biological body clock could result in more successful outcomes, reduced treatment time, and enhanced patient comfort.

The present review aims to integrate evidence from chronobiology, bone research, and orthodontics to propose a conceptual framework for chrono-orthodontics. By highlighting potential mechanisms, clinical implications, and avenues for future investigation, this work underscores circadian biology as a novel and promising dimension in orthodontic science.

2. Circadian Biology: An Overview

2.1 Central and Peripheral Clocks

A centralized pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN) directs circadian rhythms. The SCN transmits neuronal and hormonal signals to peripheral tissues to synchronize daily physiological processes to the external light-dark cycle (Mohawk et al., 2012). Peripheral clocks exist in almost every tissue, all types of bone, muscle, and oral tissues, and serve as local oscillators for controls unique to individual cells. The oscillators work via a transcription–translation feedback loop, biological rhythms that include essential clock genes; PER and CRY proteins behave as negative regulators which create regular cycles of gene expression, whereas CLOCK and BMAL1 act as transcriptional activators (Partch et al., 2014). When these molecular oscillators are disrupted, either by genetic modifications or modifiers from the environment like variable sleep cycles, tissue homeostasis and remodeling may be disturbed.

2.2 Hormonal Rhythms Relevant to Orthodontics

Several systemic hormones that influence bone biology and orthodontic tooth movement exhibit circadian rhythmicity:

- Cortisol: Levels peak in the early morning and decline throughout the day. Cortisol regulates stress response, immune modulation, and bone metabolism, with elevated levels enhancing bone resorption and influencing inflammatory mediator activity (Zvonic et al., 2006).
- Melatonin: Secreted primarily at night, melatonin exerts antioxidant, anti-inflammatory, and bone-protective effects. It enhances osteoblast differentiation, reduces osteoclastogenesis, and may play a role in regulating periodontal tissue homeostasis (Cutando et al., 2008).
- Parathyroid Hormone (PTH): Exhibits diurnal oscillation with intermittent peaks. PTH is central to calcium homeostasis and bone turnover, with rhythmic fluctuations influencing bone remodeling dynamics and responsiveness to mechanical loading (Iwaniec and Turner, 2016).

The rhythmic secretion of these hormones suggests that the biological environment for orthodontic tooth movement is not static, but fluctuates with time of day. This highlights the potential importance of timing orthodontic interventions in synchrony with hormonal activity.

2.3 Relevance to Dentistry

Oral and periodontal tissues show cellular and molecular activity that changes with the time of day, just like other peripheral systems. Mineral deposition, collagen metabolism, fibroblast proliferation, and inflammatory cytokine release have all been found to exhibit regular patterns, which are critical for periodontal remodeling and orthodontic biomechanics (Oyama et al., 2020). The circadian regulation of salivary secretion, microbial activity, and pain sensitivity may also have an effect on orthodontic responses and oral health.

These findings collectively demonstrate the biological feasibility of integrating circadian biology into orthodontics, establishing the groundwork for the recently developed concept of chrono-orthodontics.

3. Circadian Regulation of Bone Remodeling

The closely coordinated activities of osteoblasts, which create new bone, and osteoclasts, which degrade existing bone, govern the dynamic process of bone remodeling. This balance preserves skeletal integrity while enabling adaptive responses to mechanical and metabolic demands. There is mounting evidence that circadian oscillations, which are regulated by systemic hormones as well as intrinsic molecular clocks within bone cells, have an impact on bone remodeling.

Osteoclastogenesis, the process by which osteoclasts are formed and activated, varies significantly throughout the day. The increase in osteoclast activity and markers of bone resorption during the resting (night) phase in mouse models suggests a window of increased catabolic activity (Fujihara et al., 2018). Conversely, osteoblast activity peaks during the active phase, when melatonin secretion increases, encouraging osteoblast development and mineralization (Fu et al., 2019). Together, these findings demonstrate that the phases of bone resorption and production take place at distinct times, which may support the regular turnover required for skeletal homeostasis.

The molecular regulation of bone cells depends on core circadian clock genes. Mutations or deletions in genes like BMAL1 or PER2, which disrupt circadian signaling, cause skeletal abnormalities like altered bone mass, poor bone formation, and remodeling deficits (Samsa et al., 2016). These findings demonstrate the molecular and genetic links between circadian clocks and skeletal biology.

These findings have significant orthodontic implications. Since orthodontic tooth movement depends on the remodeling of alveolar bone in response to applied stresses, the timing of force application may have an impact on the rate and quality of treatment. By using orthodontic forces during periods of increased osteoclast or osteoblast activity, it may be possible to decrease side effects like root resorption, shorten treatment times, and increase the efficiency of tooth movement. Investigating chrono-orthodontics, a field where biological time is regarded as an essential part of therapy planning, is based on this point of view.

4. Circadian Influence on Orthodontic Tooth Movement (OTM)

Orthodontic tooth movement (OTM) is governed by a complex interplay between mechanical forces, bone remodeling, and inflammatory signaling. Increasing evidence indicates that this process is modulated by circadian rhythms, which influence not only bone biology but also inflammation and pain sensitivity.

4.1 Experimental Animal Studies

Research on animals provides compelling evidence that the circadian timing of orthodontic force application alters the rate of OTM. Oyama et al. (2020) demonstrated in rat models that orthodontic forces applied during the active stage of the animals' lives resulted in a notably greater amount of tooth movement than forces applied during the resting phase. These findings show how the biological response to mechanical loading varies with time, and they suggest that planning orthodontic procedures for when inflammation and metabolic reactivity are higher may speed up treatment results.

4.2 Inflammatory Mediator Rhythms

Inflammatory mediators are an essential part of the cascade that drives orthodontic tooth movement. Prostaglandins, tumor necrosis factor- α (TNF- α), and interleukin-1 β (IL-1 β) are among the cytokines that regulate bone resorption and osteoclast recruitment in the periodontal ligament. It's interesting to note that these mediators' expression and activity fluctuate throughout the day (Oishi et al., 2006). The reason why OTM rates fluctuate throughout the day may be explained by this type of rhythmicity. The efficiency of tooth movement may therefore be enhanced by applying force during pro-resorptive cytokine activity peaks, but force application during trough phases may result in delayed biological reactions.

One of the most common concerns during orthodontic treatment is pain, which directly affects patient compliance and quality of life. According to studies, orthodontic discomfort is more severe at night and in the evening, indicating that pain perception changes with the time of day (Villarreal et al., 2003). This pattern is consistent with the circadian modulation of nociceptive thresholds, neuroendocrine signaling, and prostaglandin release. This discrepancy suggests that, from a therapeutic perspective, the optimal time to turn on the appliance and give analgesics would be to lessen patient discomfort. Patient satisfaction and treatment compliance may be improved, for instance, by using force earlier in the day or modifying analgesic dosages to take diurnal pain sensitivity into account.

5. Chronotherapy in Orthodontics

Chronotherapy, a new medical paradigm, adapted treatment to the body's natural biological rhythms to optimize therapeutic efficacy and minimize side effects (Smolensky et al., 2016). Its application in orthodontics is still largely unknown, despite extensive research in the domains of pharmacology, endocrinology, and cancer. Orthodontics presents a unique opportunity to integrate chronotherapeutic concepts into clinical practice because the clock controls bone remodeling, inflammatory mediator release, and pain perception.

5.1 Force Application Timing

The orthodontic force application schedule may have an effect on the biological efficiency of tooth movement. Experimental evidence suggests that forces applied during times of increased osteoclastic activity promote faster OTM compared to rest-phase application (Oyama et al., 2020). When it comes to clinical use, orthodontists may schedule appliance activations or modifications to coincide with times when the circadian rhythm shows increased bone receptivity.

Appliance wear schedules might also be reexamined. For example, the biological effects of aligner treatment or intermaxillary elastics prescribed for nocturnal versus daytime usage may vary depending on whether peak osteoclastic or osteoblastic activity is involved. Further clinical research is needed to determine whether timing procedures could significantly reduce treatment duration.

5.2 Drug Delivery

Pharmacological adjuncts to orthodontics, particularly analgesics, are also subject to circadian influences:

- By preventing prostaglandin synthesis, non-steroidal anti-inflammatory drugs (NSAIDs), which are commonly used to treat orthodontic pain, may inadvertently slow OTM. Although patients may find it more comfortable to take NSAIDs in the evening, when pain is typically at its worst, care must be taken to avoid lowering peak prostaglandin-mediated remodeling (Krishnan, 2007).
- Melatonin supplements: Studies have shown that melatonin increases osteoblastic differentiation, inhibits osteoclastogenesis, and reduces oxidative stress, all of which support bone formation and periodontal health (Cutando et al., 2008). Although human clinical data is currently lacking, prompt supplementation may help orthodontic patients experience positive bone remodeling.

These examples underscore the importance of aligning drug administration with circadian physiology to maximize benefit while preserving remodeling dynamics.

5.3 Appliance Design

Apart from scheduling, chrono-orthodontics may benefit from recent advancements in smart appliance technology. Advances in digital orthodontics and biomaterials could result in appliances that release biomodulators or apply forces based on circadian cycles. Aligners equipped with micro-reservoirs or chrono-responsive polymers, for instance, could alter force release over the course of a day to correspond with biological windows of peak remodeling activity. Additionally, biofeedback devices could use physiological monitoring to modify force intensity in real time. Even though they are still in their infancy, these technologies demonstrate how chronobiology can be incorporated into appliance design to bring in a new era of customized, rhythm-sensitive orthodontics.

6. Clinical Implications

Integrating circadian biology into orthodontic practice holds promise for enhancing treatment outcomes and improving patient experience. While the concept of chrono-orthodontics remains in its early stages, several potential clinical implications can be envisioned:

6.1 Treatment Efficiency

Aligning orthodontic force application with phases of heightened osteoclastic and osteoblastic activity may accelerate orthodontic tooth movement. By scheduling appliance activations or adjustments during biologically favorable circadian windows, clinicians could potentially shorten treatment duration without increasing force magnitude.

6.2 Pain Management

Circadian modulation of nociceptive thresholds suggests that pain intensity fluctuates across the day, often peaking in the evening. Designing personalized analgesic regimens that anticipate these circadian pain peaks may improve patient comfort and compliance while avoiding excessive medication use.

6.3 Minimization of Adverse Effects

Optimized timing of orthodontic interventions may also help reduce biological side effects. For instance, force application during periods of balanced remodeling activity could lower the risk of external root resorption, periodontal inflammation, or tissue hyalinization, which are linked to excessive or poorly synchronized biological stress responses.

6.4 Patient-Centered Care

Chronotherapy offers opportunities for a more individualized approach to orthodontics, moving beyond “one-size-fits-all” protocols. By integrating circadian considerations into treatment planning—such as appliance wear schedules, drug administration timing, or activation intervals—orthodontic care can be tailored to each patient’s biological rhythms, lifestyle, and compliance patterns.

7. Research Gaps and Future Directions

Although the integration of circadian biology into orthodontics presents exciting possibilities, the field is still in its infancy. Several critical gaps must be addressed before chrono-orthodontics can be translated into routine clinical practice:

7.1 Human Clinical Trials

The effects of circadian timing on appliance wear schedules and orthodontic activations have not yet been fully investigated in randomized controlled clinical trials. The bulk of the evidence currently available comes from animal studies, which are helpful but fall short in explaining the variability of human circadian cycles and lifestyle factors. Carefully thought-out clinical studies are required to verify whether circadian-based procedures can improve patient outcomes or reduce treatment duration.

7.2 Biomarker Studies

Patients undergoing orthodontic treatment need to have their circadian markers tracked over a long period. These markers include salivary melatonin, cortisol, and bone turnover indicators like osteocalcin and CTX. This information may reveal the patterns of inflammation and bone remodeling in humans. It can also help identify the best times for intervention.

7.3 Chrono-Appliance Innovation

Future orthodontic appliances could feature programmable, time-sensitive force-release mechanisms. Advances in digital monitoring, smart polymers, and micro-reservoirs may allow these appliances to deliver biomodulators or forces that match circadian rhythms. This could improve biological efficiency and lower side effects. Research in translational bioengineering is showing promise in this area.

7.4 Interdisciplinary Research

Collaboration among chronobiologists, orthodontists, and materials scientists is necessary to improve chrono-orthodontics. By connecting practical orthodontics with molecular chronobiology, this teamwork can foster progress in clinical procedures and device design.

8. Conclusion

In orthodontic research, circadian biology offers new opportunities to improve the biological and clinical aspects of treatment. By using the ideas of chronotherapy, orthodontists might provide more personalized care, reduce side effects, and achieve quicker and more effective tooth movement. Current evidence from molecular and animal studies strongly supports this approach. However, well-planned human clinical trials are needed to bring it into standard practice. To start an era of personalized, rhythm-sensitive orthodontic care, the future of orthodontics may depend on aligning biomechanical treatments with the body’s circadian clock, its most basic rhythm.

Hormone/Factor	Circadian Peak	Biological Role	Orthodontic Relevance
Cortisol	Early morning	Regulates stress, inflammation, bone resorption	May influence OTM rates
Melatonin	Night	Promotes osteoblast activity, inhibits osteoclasts	Enhances bone formation, reduces resorption
PTH	Intermittent peaks	Calcium regulation, bone turnover	Regulates bone remodeling during OTM

Prostaglandins (PGE ₂)	Evening	Mediators of inflammation and pain	Affect OTM rate and pain variation
Growth Hormone	Night (during sleep)	Stimulates bone formation and repair	Potential role in enhancing OTM

Table 1. Key circadian-regulated hormones and their relevance to orthodontics

Area of Application	Chronotherapy Concept	Clinical Implication
Force application	Timing activations with osteoclastic activity	Accelerates OTM
Aligner wear	Prescribing wear aligned with rhythms	Improves aligner efficiency
Pain management	NSAID dosing aligned with circadian nociception	Optimizes pain relief
Biomarker monitoring	Tracking salivary melatonin/cortisol	Personalizes treatment response
Smart appliances	Time-sensitive force/drug release	Enhances treatment precision

Table 2. Potential clinical applications of chrono-orthodontics

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