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Chronobiology in Orthodontics – A Literature Review

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Abstract

The biological clock regulates nearly every physiological function of the body through a 24-hour circadian rhythm controlled by the suprachiasmatic nucleus (SCN). Core clock genes such as CLOCK, BMAL1, PER, and CRY form transcriptional–translational feedback loops (TTFL) that synchronize cellular and hormonal activities. In dentistry, particularly orthodontics, circadian rhythm plays a vital role in bone remodeling, pain perception, and craniofacial growth. Hormones such as cortisol, growth hormone, and vitamin D, along with cytokines and interleukins, exhibit rhythmic secretion patterns that regulate osteoblastic and osteoclastic functions, thereby influencing tooth movement and post-treatment stability. Moreover, variations in circadian rhythm affect pain sensitivity, bone formation, and inflammatory responses, all of which impact orthodontic outcomes. Recognizing these time-dependent biological variations can help in optimizing the timing of force application and improving treatment efficiency. A deeper understanding of chronobiology may thus enable clinicians to align orthodontic therapy with the body's natural rhythms, enhancing biological response, patient comfort, and long-term stability.

Keywords: Chronobiology, Circadian Rhythm, Orthodontic Tooth Movement, Bone Remodelling, Vitamin D, Cortisol, Melatonin, Growth Hormone, Pain Perception; Chronotherapy.

Introduction

The term "circadian rhythm" refers to the rhythm that is present in the biological activity of living things, including behavioral, physiological, and biochemical

processes. The word "circadian rhythm" refers to the pattern or rhythm that the body follows throughout the day because the Greek words "circa" and "diam" mean "around" and "day," respectively.[1] To put it simply, these are known as the biological clock, and they sustain nearly every function, starting at the molecular level, on a regular 24-hour period. Although the exact process is yet unknown, the suprachiasmatic nucleus is thought to be the primary element in controlling the circadian rhythm. Peripheral clocks, on the other hand, are a few organs and tissues that are thought to likewise fluctuate the circadian rhythm. Certain clock genes, which are found in practically every cell in the body, interact endogenously with these core and peripheral components. Certain environmental factors known as "zeitgebers" and photic factors, such as sunlight, have an impact on these clock genes.[2,3]Also the genetic makeup and cognitive abilities of the individual is vital in determining the circadian typology.[4] Accordingly, when the rhythm corresponds with the outside stimuli, the human body is said to be entrained. [5] The suprachiasmatic nucleus' humoral signals and behavioral processes including sleep, food consumption, body temperature, and energy metabolism are also considered peripheral components.

Any desynchronization in this chronobiology would lead to suboptimal functioning of bodily processes and thereby affecting the human health.[6] The major desynchronization occurs during altered sleep-wake cycle especially in the night shift workers,[7] which directly or indirectly affects the food consumption, physical activity and certain other environmental cues. From various studies in the oral health sciences, it is evident that this circadian rhythm also influences the oral tissues thereby regulating enamel formation, [8] teeth eruption, bone metabolism, periodontal cellular remodeling, and even salivary secretion. Molecular clocks that act over longer timescales may play a role in chronic conditions such as cancer. Their functions, however, are still poorly understood in oral biology and dentistry. Early evidence suggests these clocks may also influence aging and could have applications in forensic science.[9]

Orthodontic tooth movement is a biologically regulated process involving complex interactions among bone remodeling, inflammatory mediators, and neurosensory pathways—all of which exhibit temporal variations influenced by circadian rhythms. Chronobiology, the science of biological timekeeping, explores how physiological processes fluctuate over a 24-hour period in response to internal molecular clocks and environmental cues such as light and temperature.

In the context of orthodontics, circadian regulation has been shown to influence bone metabolism, hormonal secretion, inflammatory responses, and pain perception[10]—all critical components of orthodontic treatment. These rhythmic oscillations are coordinated primarily by the suprachiasmatic nucleus (SCN), the central pacemaker located in the hypothalamus, which synchronizes peripheral clocks in tissues including the periodontal ligament (PDL) and alveolar bone. [11,12]

Understanding these rhythmic patterns offers a new perspective in orthodontics: optimizing treatment timing, predicting biological responses, and enhancing patient comfort through chronotherapeutic strategies. Emerging evidence suggests that the rate of tooth movement, tissue remodeling efficiency, and even the magnitude of orthodontic pain may vary depending on the time of day when mechanical forces are applied.

This review aims to synthesize current evidence on the chronobiological aspects of orthodontics, focusing on its implications in pain perception, orthodontic tooth

movement, craniofacial growth modulation, and other clinical outcomes.

Chronobiology and Its Molecular Mechanisms

Chronobiology deals with the study of biological rhythms and their temporal organization. The circadian rhythm, the most prominent of these, is maintained through transcriptional–translational feedback loops involving clock genes and their protein products. In mammals, the central pacemaker is located in the suprachiasmatic nucleus (SCN), which synchronizes peripheral clocks in tissues such as bone, muscle, and periodontal ligament through neural and hormonal pathways. [3]

At the molecular level, the circadian system operates through a core set of genes, including CLOCK, BMAL1 (ARNTL), PER (PER1, PER2), and CRY (CRY1, CRY2). The CLOCK–BMAL1 heterodimer binds to E-box elements in the promoter regions of Per and Cry, initiating their transcription. As PER and CRY proteins accumulate in the cytoplasm, they form complexes that re-enter the nucleus to inhibit their own transcription by repressing CLOCK–BMAL1 activity, forming a ~24-hour oscillation. [13,14] This primary loop is further stabilized by auxiliary feedback involving Rev-Erbα, RORα, and post-translational modifications such as phosphorylation, acetylation, and ubiquitination that fine-tune protein stability and degradation. [15]

Beyond these “core clock” genes, clock-controlled genes (CCGs) regulate a wide range of physiological processes, including inflammation, metabolism, and bone turnover. Several bone-related genes such as RUNX2, BMP2, Osteocalcin (BGLAP), and Osteopontin (SPP1) display rhythmic expression patterns. [16] These oscillations directly influence osteoblast and osteoclast activity, thereby impacting bone remodeling relevant to orthodontic tooth movement.

Recent studies have demonstrated circadian rhythmicity in periodontal ligament (PDL) fibroblasts, where synchronization using dexamethasone revealed oscillatory expression of ARNTL, CLOCK1, PER1, and PER2. These rhythms were accompanied by fluctuations in bone remodeling markers such as RANKL, OPG, RUNX2, and COL1A1, suggesting that mechanical stress during orthodontic force application may be modulated by intrinsic circadian mechanisms. [17,18,19]

Furthermore, BMAL1 has emerged as a crucial mediator in the mechanotransduction of orthodontic forces. Xie et al. [20] demonstrated that orthodontic force application activates the ERK/AP-1 signaling pathway in PDL cells, leading to increased BMAL1 expression. This, in turn, promotes RANKL and CCL2 secretion, facilitating osteoclast recruitment and bone resorption on the compression side. Inhibition of BMAL1 expression significantly reduced osteoclastic activity and tooth movement in vivo, confirming its vital role in orthodontic bone remodeling.

The CLOCK gene has also been shown to regulate bone formation via PDIA3, a receptor for active vitamin D. CLOCK-deficient mice exhibited reduced bone density and increased osteoblast apoptosis, highlighting the clock’s role in osteoblast survival and differentiation. [21] Collectively, these findings support that circadian regulatory proteins influence bone remodeling through temporally coordinated molecular signaling, directly affecting the rate and efficiency of orthodontic tooth movement. The overall molecular mechanism of the transcriptional–translational feedback loops (TTFL) of clock-controlled genes and their role in the orthodontic tooth movement is depicted in Figure 1.

Chronobiology and Tooth Movement

Orthodontic tooth movement is a complex reactionary effect in bone remodeling that is mediated by series of

inflammatory reactions on force application. This complex activity occurs by alternate bone deposition by osteoblast and bone resorption by osteoclasts. Vitamin D, growth hormone, melatonin and cortisol are certain important hormones that regulates the mineral deposition and inflammatory regulations. All these hormones depict a rhythmic pattern which influences their production as well. A study revealed that orthodontic tooth movement shows diurnal variation, with forces applied during the rest (light) period producing nearly twice the tooth movement and greater bone formation than those applied during the active (dark) period. [22]

Vitamin D, Chronobiology and Tooth Movement

Vitamin D activates both the resorbing and bone forming cells. Vitamin D influences the expression of signaling molecules in the RANK/RANKL/OPG [23] system, a key regulator of bone remodeling. Calcitriol, the active form of vitamin D increases the osteoclastic activity which results in bone resorption in the initial stages of tooth movement followed by a phase of bone deposition by the osteoblasts. Vitamin D is thus essential in maintaining the amount of bone remodeling during the orthodontic tooth movement. Certain studies provide evidence of accelerating tooth movement by administration of Vitamin D and there are few contradictory results showing no statistically significant difference in the rate of tooth movement. Vitamin D-binding protein (DBP) involved in vitamin D transport and mobilization exhibits a strong circadian rhythm and some receptors are present in the SCN suggesting a strong role in the circadian rhythm. Vitamin D also has a seasonal effect where vitamin D is produced more in summer compared to winter. [24,25] Thus, it is evident that bone remodeling has a certain circadian rhythm in which the peak orthodontic tooth movement occurs during the resting period especially in the evenings and nights for humans.

Melatonin, Chronobiology and Tooth Movement

Melatonin, a neurohormone primarily secreted by the pineal gland, plays a pivotal role in regulating the circadian rhythm and maintaining physiological homeostasis. Its synthesis is influenced by the light–dark cycle, with peak secretion occurring at night. [26] At the molecular level, melatonin is synthesized from tryptophan through a series of enzymatic reactions involving tryptophan hydroxylase, aromatic L-amino acid decarboxylase, arylalkylamine N-acetyltransferase (AANAT), and hydroxyindole O-methyltransferase (HIOMT), leading to the final production of N-acetyl-5-methoxytryptamine, commonly known as melatonin. [27] (Cardinali and Pévet,1998). The circadian expression of the AANAT gene is under the control of the suprachiasmatic nucleus (SCN). The SCN receives light cues from the retina and relays signals through the sympathetic nervous system to the pineal gland, increasing cyclic AMP levels and promoting AANAT expression during darkness. [28] (Claustrat et al., 2005). Consequently, melatonin acts as an internal signal of night, synchronizing peripheral tissues and influencing metabolic, endocrine, and skeletal processes. [29]

Beyond its chronobiotic effects, melatonin exhibits strong antioxidant, anti-inflammatory, and bone-protective properties. It enhances osteoblastic activity through Runx2 and BMP-2 pathways while concurrently reducing osteoclastic bone resorption as well as root resorption via down regulation of the RANK/RANKL/OPG signaling pathway. [30,31] This dual action promotes bone formation and helps preserve alveolar bone and periodontal ligament (PDL) integrity. [32,33]

In orthodontics, where bone remodeling is essential for tooth movement, melatonin's regulatory role becomes particularly relevant. Experimental studies have shown

that melatonin administration in male Wistar rats increased alkaline phosphatase (ALP) activity and decreased interleukin-6 (IL-6) levels, indicating enhanced osteoblastic activity and reduced osteoclastic differentiation. [34] By reducing IL-6 levels, melatonin also alleviates pain perception associated with orthodontic tooth movement.

Furthermore, melatonin's inhibitory effect on osteoclasts can help minimize root resorption resulting from excessive orthodontic forces.[35] Its anti-inflammatory action and bone-preserving potential make it valuable during the retention phase, where it may reduce relapse by stabilizing alveolar bone and PDL remodeling. These properties are also beneficial in periodontally compromised[36] or systemically affected patients, such as those with diabetes, where bone metabolism is impaired. [37]

Since melatonin secretion follows a circadian pattern—being highest at night [38,39] its physiological surge may influence the rate of orthodontic tooth movement. Interestingly, patient compliance in wearing removable orthodontic appliances tends to be higher during nighttime, coinciding with increased melatonin levels. Depending on whether melatonin exerts a net inhibitory or stimulatory effect on tooth movement, its rhythmic secretion could have therapeutic implications for optimizing appliance wear timing.

Chronobiology, Cortisol and Tooth Movement

Cortisol, the principal glucocorticoid secreted by the adrenal cortex, follows a distinct circadian rhythm characterized by peak levels in the early morning and a gradual decline toward midnight. [40] This secretion is governed by the hypothalamic–pituitary–adrenal (HPA) axis, under the influence of the suprachiasmatic nucleus—the body's master circadian pacemaker. [41] Cortisol plays a dual role in bone metabolism: while physiological levels are essential for maintaining normal bone turnover, elevated or prolonged exposure can suppress osteoblastic differentiation, reduce collagen synthesis, and enhance osteoclastic resorption, leading to bone loss. [42,43,44]

In orthodontics, tooth movement depends on the dynamic equilibrium between bone resorption and deposition around the periodontal ligament (PDL). Variations in cortisol levels, both circadian and stress-induced, can influence this remodeling process. Elevated cortisol during the daytime promotes osteoclastic activity, potentially accelerating tooth movement but also increasing the risk of root resorption and periodontal strain. [45,46] In contrast, low cortisol levels during the night may favor osteoblastic and reparative activity, supporting bone formation and tissue recovery. Furthermore, cortisol modulates inflammatory mediators such as prostaglandins and interleukins, which play key roles in initiating the orthodontic tooth movement cascade. [47] Zhou et al.[48] reported that synchronizing orthodontic force application with circadian peaks in bone metabolic activity could enhance treatment efficiency. Similarly, Chan[49] highlighted that dysregulation of cortisol rhythms—often resulting from stress or sleep disturbances—may disrupt bone turnover and prolong treatment duration.

Understanding the rhythmic interplay between cortisol secretion and bone metabolism offers valuable clinical insight. Timing orthodontic adjustments or force activations during phases of reduced cortisol activity may help minimize pain perception and soft tissue inflammation while maintaining controlled tooth movement. Conversely, disturbed sleep or chronic stress—which dysregulate cortisol rhythms—can hinder normal bone remodeling, prolong treatment time, and heighten the risk of adverse outcomes. Maintaining

circadian balance through adequate sleep, stress management, and lifestyle regulation may therefore indirectly enhance orthodontic efficiency and patient comfort.

Chronobiology in Growth of Jaws

Growth hormone (GH) secretion follows a distinct circadian rhythm, with peak levels occurring during the dark phase of the daily cycle, typically coinciding with deep sleep[50,14]. This nocturnal surge in GH plays a vital role in stimulating cellular proliferation, protein synthesis, and bone growth, thereby influencing craniofacial and mandibular development. Disruption of the natural sleep–wake pattern, as seen in shift workers or individuals with irregular sleep schedules, leads to compensatory and unpredictable GH pulses during the daytime. [51,522] These findings indicate that GH secretion is not governed solely by the sleep–wake cycle but also modulated by intrinsic circadian mechanisms regulated at the hypothalamic level.

The GH and functional appliance group had significantly greater mandibular length, thickness of condylar cartilage, and expression of matrix metalloproteinases MMP-1, MMP-13, Col II, and Col X in the cartilage than the other groups.[52,53,54,55] GH could increase head circumference growth and anterior facial height, influence growth pattern, and regulate mandibular and condylar growth and remodeling. Injection of GH has been used clinically for the treatment of short-stature children and those having retrognathic mandible. Administration of growth factors along with mandibular repositioning appliances have an almost twofold effect on the induced expression of MMP-1 and MMP-13[56] in comparison with the administration of mandibular repositioning appliances only. MMP-1 and MMP-13 are important proteases in cartilage remodeling and mineralization in physiological conditions,[57] which play an important role in the transformation from cartilage into bone, as well as the formation of primary calcification centers and blood vessels during bone reconstruction. Similarly, growth hormone when administered with fixed functional appliance have the same effect of inducing more mandibular growth compared to the controls in which only fixed functional appliance is given. [58] Hence, when growth hormone administered night time during functional appliance therapy enhances the growth of jaws.

Growth hormone also influences the orthodontic tooth movement by regulating the bone metabolism. It stimulates insulin like growth factor (IGF-1) which accelerates the orthodontic tooth movement and in the same time it delays the production of collagen which hinders the stability of bone to the new attained position. Aligning orthodontic or functional appliance therapy with the nocturnal GH surge may enhance skeletal adaptation and treatment efficiency, highlighting the clinical importance of chronobiological synchronization in orthodontic growth modification.

Chronobiology and Pain Perception

Orthodontic pain is a common experience during various treatment procedures, including separator placement, initial wire engagement, banding, wearing elastics, rapid maxillary expansion, and debonding [59,60] (Panda et al., 2015; Baldini et al., 2015). The pain typically begins around 12 hours after applying orthodontic force, peaks within 24 hours, gradually subsides over 3–7 days, and returns to baseline levels after approximately one month. [61] Animal studies have indicated that orthodontic pain can elicit emotional stress and transient learning and memory impairments. [62] The primary cause of orthodontic pain is inflammatory vascular occlusion, which triggers the release of inflammatory mediators and immune cells, leading to neurogenic inflammation. These

mediators activate sensory receptors in response to mechanical orthodontic stimuli, resulting in nociceptive pain. [63]

Orthodontic pain perception exhibits a distinct diurnal variation, influenced by fluctuations in β-endorphins and interleukin levels within plasma and brain tissues. Pollmann[64] reported that dental pain threshold follows a circadian rhythm—highest in the afternoon (least pain intensity) and lowest at night (greatest pain intensity). Disruption of the circadian rhythm has been shown in various animal studies to reduce the pain threshold, thereby increasing perceived pain intensity. Consequently, chronotherapy strategies such as maintaining a regular sleep–wake cycle, minimizing artificial light exposure at night, and adhering to properly timed meals may help mitigate dental sensitivity, soreness, and discomfort during orthodontic tooth movement.

Further supporting the role of circadian rhythms in orthodontic pain, it is observed that β-endorphin and interleukin levels exhibit daily variations[65], which correlate with pain perception. Profound and prolonged local anesthesia could be achieved when injected in the evening which can be utilized during orthodontic teeth extraction also. [66] Optimized timing of appliance activation during orthodontic procedures and drug delivery in alignment with the body's natural circadian rhythms may help reduce pain and improve overall treatment outcomes. This approach highlights the promise of chronotherapy in making orthodontic care more comfortable and biologically efficient for patients. [66]

Clinical Implications and Future Directions

Chronobiology plays a crucial and complex role in nearly all physiological and biological activities of the body. Chronotherapy refers to behavioral or clinical interventions that align medical or dental treatments with the body's master clock—the circadian rhythm. Such interventions include maintaining regular sleep–wake cycles, adhering to consistent meal timings, minimizing artificial light exposure at night, and ensuring adequate daylight exposure. [67] These measures not only enhance the efficacy of orthodontic therapy but also improve the overall quality of life. In orthodontics, understanding and applying the chronobiological principles could lead to more efficient tooth movement, reduced pain and root resorption, accelerated treatment, and improved post-treatment stability during the retention phase, potentially minimizing the risk of relapse. The integration of chronotherapy in orthodontics may also support jaw and dentoalveolar growth in adolescents when combined with functional or orthopedic appliances.

Despite its potential, there is currently limited research in orthodontics directly linking chronobiology to treatment outcomes, and few studies provide strong evidence for the clinical application of chronotherapy. Investigating chronobiological effects in humans is challenging due to numerous confounding factors, including individual behavioral patterns, lifestyle differences, and environmental influences. Long-term studies that rigorously control for sleep patterns, meal timings, and light exposure are necessary to evaluate the true benefits of chronotherapy, but such interventions are often difficult to implement practically. Nonetheless, the concept of "chronotype profiling" holds promise for developing personalized [68], time-optimized orthodontic strategies that could enhance both clinical outcomes and patient experience.

Though it is difficult to track daily routine activities of an individual, artificial intelligence and sensors to detect the sleep cycle and other activities can be utilized in the near future.

Conclusion

Chronobiology influences almost every process in the human body, and orthodontics is no exception. Understanding how biological rhythms affect bone remodeling, pain perception, and growth, we can leverage the dynamic biological environment to a maximum therapeutic effect. By aligning orthodontic care with the body's natural timing through proper sleep, nutrition, and light exposure—clinicians can enhance tooth movement efficiency, reduce discomfort, and improve long-term stability after treatment.

However, the link between chronobiology and orthodontics is still not fully explored. Most available studies are experimental or animal-based, and applying these findings in daily clinical practice remains challenging. Factors like individual sleep patterns, lifestyle, and stress responses can vary widely among patients. Future research that connects chronobiological data with molecular and clinical findings could help design more personalized, time-based treatment strategies. With deeper understanding, chronotherapy has the potential to make orthodontic care more biologically efficient, comfortable, and predictable for every patient.

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Abbreviations

CLOCK- Circadian locomotor output cycles kaput

BMAL-1- Brain and muscle aryl hydrocarbon receptor nuclear translocator 1

ARNTL- aryl hydrocarbon receptor nuclear translocator-like protein 1

PER- period 1-3

CRY- Cryptochrome

ROR- Retinoic acid-related orphan receptor

Rev-Erbα- Member of Nuclear receptor subfamily 1 group D

ERK/AP-1- extracellular signal-regulated kinase (ERK)/ Activator protein 1 (AP-1)

SCN- Suprachiasmatic nucleus

RANK- Receptor activator of nuclear factor kappa

RANKL- Receptor activator of nuclear factor kappa beta ligand

OPG- Osteoprotogerin

MMP- Matrix metalloproteinases

GH- growth hormone

Figure 1:

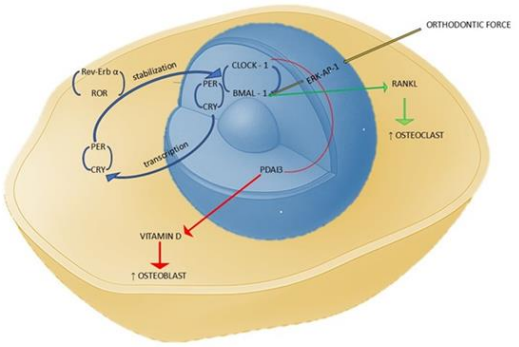

Figure 1. *Molecular mechanism of chronobiology and its interaction in orthodontic tooth movement.* Blue arrows indicate transcriptional–translational feedback loops (TTFL) of core clock genes. The red and green lines represent circadian rhythmic patterns in vitamin D–mediated osteoblastic activity and RANKL-driven osteoclastic activity, respectively.