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Chronodentistry through orthodontic perspective: A literature review

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Abstract

The human body possesses a unique set of machinery called the molecular/biological clocks that function on a regular 24-h basis forming a circadian rhythm (CR). This aids in coordinating the human biological system with ever-changing environmental conditions, thereby maintaining a balance in its functioning. The central/core component of this system is known to be in the suprachiasmatic nucleus of the hypothalamus with a few aides in the periphery. The periodontal ligament in humans, being one of the dynamic oral tissues, has been shown to exhibit this self-sustained, innate oscillatory behavior that has gained significant attention from dental surgeons. Though substantial evidence regarding its precise role in maintaining circadian periodicity is still unclear, its indispensable role in dentofacial functioning cannot be denied. This review is an attempt in bringing to light the possible role of circadian periodicity in the functioning of oral tissues in the field of orthodontics with a special focus on its role in bone remodeling, orthodontic tooth movement, orthopedic and functional appliances, pain management, and their clinical implications. This could provide a better understanding of the various physiologic and pathologic processes and help us refine our approach toward orthodontic diagnosis and therapeutics. This review would therefore serve as an overview, opening more avenues for further research on this topic that can greatly help the orthodontic fraternity.

Keywords:

Chronodentistry, circadian rhythm, diurnal variation, orthodontics

Introduction

The human body possesses a unique ability to coordinate the biological system with constantly changing environmental conditions. This process is orchestrated utilizing the machinery called the molecular/biological clocks that act on a regular 24-h basis forming a circadian rhythm (CR).

The central component of the master biological clock is situated in the suprachiasmatic nucleus of the hypothalamus with a few other subordinates in the periphery.[1] On receiving inputs (also called zeitgeber) that may be in the form of light, change in body temperature, food, etc., the circadian clock acts to give outputs in synchrony with various physiological processes.[2] Within our body, the connecting link between the brain and peripheral organs is provided by a large number of genes that coordinate a variety of metabolic and physiological processes. Various attempts have been made to extensively study the molecular mechanism of this circadian clock implied in both physiologic and pathologic states and it has been found that the basis of this clock is a transcriptional–translational feedback loop (TTFLs).[3,4]

The core component of the mammalian circadian clock is formed by proteins such as circadian locomotor output cycles kaput (CLOCK), brain and muscle aryl hydrocarbon receptor nuclear translocator 1 (BMAL1), cryptochrome 1,2 (CRY1,2), and period 1-3 (PER1-3), which interact within this feedback loop.[2] The two proteins CLOCK and BMAL1 expressed at the beginning of the day, using daylight as an input stimulus, bind to each other, form a dimer, and enter the nucleus where it binds the DNA at regulatory sequences

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called E-box. This binding promotes transcription resulting in the release of mRNAs. These mRNAs are exported out of the nucleus into the cytoplasm and get translated to proteins such as CRY, PER, and member of nuclear receptor subfamily 1 group D (Rev-Erbα). On reaching a certain level of mRNA, the protein products CRY and PER dimerize and this complex enters the nucleus and binds to the CLOCK–BMAL1 complex, thereby inhibiting their transcription in classic negative feedback. As the light of the night sets in, the PER–CRY dimer gets degraded, allowing for the activation of CLOCK-BMAL1 in a new transcription cycle [Figure 1]. This central circadian network is composed of two negative feedback loops. The first one is a hetero-multimeric complex made up of the PER–CRY proteins and casein kinase I (a key circadian regulator), which translocates into the nucleus and inhibits the activity of BMAL1–CLOCK dimer directly to limit its own transcription. The activators BMAL1 and CLOCK, which deactivate their own transcription via the *Rev-Erb* genes through an orphan receptor related to retinoic acid (ROR), are the second negative feedback loop.[1]

With the discovery of the expression of these clock genes in craniofacial tissues, multiple avenues have opened for research, especially in the field of dentistry. However, the precise functions of these respective peripheral clocks in oral tissues are yet to be understood. This review is an attempt in bringing to light the possible role of circadian periodicity in the functioning of oral tissues in the field of orthodontics with a special focus on its role in bone remodeling, orthodontic tooth movement, orthopedics, functional appliances, pain management, and their clinical implications, which would help us refine our approach toward orthodontic diagnosis and therapeutics.

Search Strategy

A computerized search was conducted using the terms "chronodentistry," "diurnal rhythm AND oral tissues," "circadian periodicity AND oral tissues," and "clock genes" in the electronic databases namely PubMed Central, Scopus, Web of Sciences, and Google Scholar. The search was limited to full-text English-language items published until 2021. Animal studies, randomized control trials, cross-sectional, prospective studies, and relevant reviews on the topic were included. A manual search of the reference lists of the included articles was carried out to uncover additional pertinent papers that the computerized search could have overlooked. Articles from the retrieved search list were grouped under various headings based on their potential application in orthodontics. These included the effect of CR on craniofacial growth and development, periodontal tissues, tooth eruption, orthodontic appliance wear, pain management, and biomaterials as discussed below.

Discussion

Circadian Rhythm and its Role in Orthodontics

Role of CR in craniofacial growth and development

It takes a complex biological process for the craniofacial skeleton to grow and develop. Various bone, cartilage, and mesenchymal cell populations work together to repair the bone through intramembranous and endochondral ossification processes. Studies have proven the indispensable role of BMAL1 in the formation of body tissues including bones, cartilage, and teeth, the evidence for which is as follows;

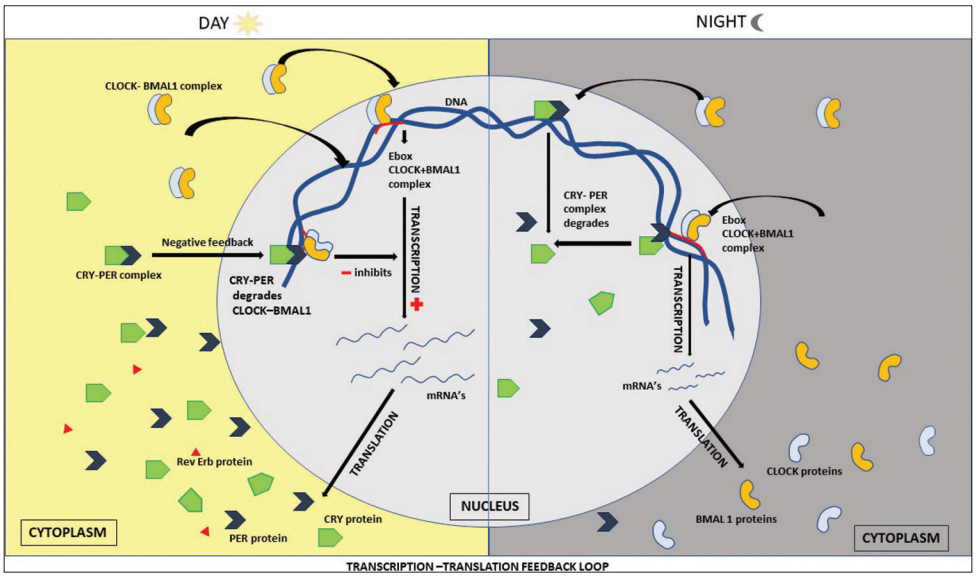

Figure 1: Graphical representation of a human cell showing a typical circadian transcription–translation feedback loop

The proliferation and differentiation of stromal cells into osteoblasts are mediated via BMAL1, which is widely expressed in mesenchymal cells differentiating to produce skeletal-related cells. It has been discovered that BMAL1 and Rev-erb control the genes that code for osteoprotegerin (OPG).[5] The action of BMAL1 on factors such as RUNX2, SOX9, Wnt, BMP, and the Hedgehog (Hh) signaling pathway is essential for the formation of bones and teeth. A higher rate of bone production, mostly at night, was consistent with the peak time of BMAL1 expression.[6] Endochondral ossification, cartilage growth, and development were disrupted by the suppression of BMAL1 in chondrocytes, leading to craniofacial abnormalities.[7] Animal studies by Zhou *et al*.[8] demonstrated lower OPG levels in BMAL1-deficient mice, which may be related to the suppression of OPG upregulation brought on by BMAL1 loss. Studies have also shown a circadian clock-mediated upregulation of ameloblastic and odontoblastic cells responsible for the development of dentition.

Clinical significance

- A substantial BMAL1 and OPG deficiency were identified in patients with skeletal mandibular hypoplasia (SMH). In their animal study, Zhou *et al*.[8] provided evidence for the potential prevention of SMH following injection of OPG, after which an increase in bone density and a decrease in osteoclastic potential was seen. Human research on the subject is, however, scarce.
- By lessening the degree of facial dysmorphism, administration of the Hh signaling activator smoothened agonist (SAG) enhanced bone repair and the loss of bone density caused by BMAL1 deficiency. Administration of Hh SAG during prepuberty and early puberty could therefore be a viable alternative to surgical procedures.
- In skeletal illnesses such as osteoarthritis and osteoporosis, BMAL1 is a potential target for curative and preventive strategies. Future success would depend on identifying these BMAL1 activators to address these disorders.[1,5,6]

Role of CR on periodontal tissues

The self-sustaining, innate oscillation mechanism or the CR is found to exist in the periodontal tissues. Although there is a lack of substantial evidence, Janjic *et al*.[9] in their study provided preliminary evidence of the existence of peripheral clock genes in PDL fibroblasts.

In a study by Hilbert *et al*.,[10] following the administration of dexamethasone, the PDL fibroblasts showed a diurnal variation in the expression of components of the circadian clock. OPG levels and BMAL1 expression were found to be inversely correlated in PDL fibroblasts. After 24 h, when compared to post-12 h, the expression of OPG and RANKL, which is essential for bone metabolism, exhibited a considerable downregulation. The transcription factor RUNX2, which is the master gene of bone formation, together with RUNX3, was found to positively regulate the hypertrophy of chondrocytes, contributing significantly to skeletogenesis. Collagenous and non-collagenous proteins of the periodontal apparatus such as osteopontin, osteocalcin, and COL1 A1 have also shown a circadian periodicity in their expression.

Through its expression in osteoblasts of the PDL, BMAL1, which is a crucial component of the CLOCK system slows bone resorption by altering the osteoblast-dependent control of osteoclastogenesis (via the RANKL–OPG axis). Previous animal studies have shown an increased bone mass with elevated bone deposition in mice lacking PER or CRY, which are the negative regulators of gene transcription mediated by the BMAL1/CLOCK complex. Takarada *et al*.[11] demonstrated diurnally alternating levels of RANKL in mice as a result of BMAL1 change. Therefore, it can be concluded that PDL fibroblasts' OPG/RANKL system is subjected to circadian regulation.

Studies have shown a correlation between CR and the formation of mineralized tissues, including bone formation and bone resorption. The orthodontic tooth movement (OTM) model in animals was used to demonstrate for the first time the *in-vivo* expression of circadian genes and osteogenic genes/proteins within the periodontal tissue, suggesting a potential role for the circadian cycle in OTM.[12]

Circadian periodicity has been discovered in other oral tissues as well, for example, in the development and functioning of salivary gland structures. Additionally, they have been linked to pathologies such as oral cancer and Sjogren's syndrome.[10]

Clinical significance

- Given that CR impacts bone production, which, in turn, regulates orthodontic tooth movement, this finding is particularly pertinent to the goals of predictive, prophylactic, and personalized medicine. Through the alteration of CR genes, improved design and delivery of orthodontic treatment can be performed.
- Considering the patient's genetic makeup and environmental factors, future studies can be designed to accelerate the rate of tooth movement by regulating peripheral oscillation.
- The role of CR and its underlying potential in influencing soft/hard tissue regeneration could be of great help in the context of maxillofacial surgery, rehabilitation, and plastic surgery.[12]
- CR has been shown to affect surgical treatment outcomes. Postoperative levels of inflammatory

markers interleukin (IL) 6 and 8 had a direct association with the time of initiation of surgical procedures. Additionally, it was shown that fibroblasts' CR does influence actin dynamics that would affect wound healing.[10]

Role of CR in tooth eruption

It has been discovered that CR influences tooth eruption, particularly during the pre-functional stage. During the pre-functional eruption stage, tooth eruption can take place either as a 1) reaction to a hormonal/metabolic cycle, 2) as a rhythmic change in the masticatory, and/or 3) soft tissue pressures that oppose eruption after reaching the functional occlusal level.[13]

In their study, Risinger and Proffit[14,15] employed a video microscopic approach to monitoring the post-emergent spurt in tooth movement and discovered that tooth eruption occurs primarily between 8 p.m. and 1 a.m. Teeth cease to erupt early in the morning, and during the day they have a slightly intrusive effect. Because the periodontal ligament has a circadian periodicity, the observed eruption in the rhythm is most likely the result of fluctuating hormone levels and their impact on the ligament. Human premolar eruption occurs in the late evening, whereas thyroid and growth hormones are normally secreted. In addition, the pattern of masticatory activity or soft tissue pressures against the teeth differs between day and night.

CR in eruption may be important in clinical orthodontics for the following reasons:[13]

- The development of an ideal occlusion is significantly influenced by tooth eruption. Most malocclusions are caused by eruptive pathway failure, which can result in situations such as crowded teeth or the impaction of teeth.
- In cases of open bite, the excessive eruption of the posterior teeth is characterized by a downward and backward rotation of the mandible. In such circumstances, managing tooth eruption by observing its periodicity is essential to effective therapy.
- Despite the absence of ankylosis, teeth do not respond to orthodontic forces in situations such as a primary failure of eruption.
- This can be caused by a disrupted circadian hormone release within the abnormal periodontal ligament.
- In the future, drugs can be administered locally or systemically to control and manipulate the rate of eruption.
- Studies have shown that growth hormones may play a role in the CR of skeletal growth, which is comparable to that of tooth eruption. Therefore, growth manipulation might be effective if carried out with a thorough understanding of these hormones' circadian periodicity.
- The enamel prism cross-striation is related to a 24-h circadian cycle in enamel matrix apposition. This suggests the role of the circadian clock in odontogenesis.

Orthodontic appliance therapy and CR

Growth modification appliances influenced chondrocyte proliferation and differentiation in the mandibular condyle. Also, a time-dependent variability was seen in the growth rates of both primary and secondary cartilages. In animals, retractive (chin cap) or protractive (Louisiana State University/LSU activator) forces were found to be more effective when used during their light periods of rest rather than during their active periods (dark period).

Other devices, such as the postural hyper propulsor, Andresen–Haupl activator, Frankel appliance, bionator, and Class II elastics, however, only exhibited their benefits when they were worn.[16] According to a study by Talvitie *et al*.,[17] the daily rhythm and timing of appliance usage had an equal impact on the efficacy of orthopedic appliance therapy as the amount of force applied.

Miyoshi *et al*.[18] demonstrated variability in orthodontic tooth movement that was dependent on the time of force application. They demonstrated in their animal model that after an initial period of orthodontic tooth movement equal to force application, the tooth movement ceased in the group kept in darkness, whereas the tooth movement continued in the control group with a regular diurnal rhythm. Additionally, compared to mice housed in regular day–night cycles, animals exposed to light for an extended period showed higher tooth movement, thereby highlighting the role of zeitgeber in circadian periodicity.

Clinical significance

- Orthodontic removable appliances and other adjuncts should be worn during the circadian therapeutic window (i.e., at night). According to Gafni *et al*.,[19] doing so not only improves patient compliance but also resulted in a positive biological impact. According to the author, the time and strength of force application are critical for operations such as distraction osteogenesis.
- Similarly, mandibular retractive force administered at rest rather than during the active period, can effectively suppress the condylar growth and cause differentiation and proliferation of chondrocytes.[20]
- Force application during the rest period can improve the efficiency of orthodontic tooth movement. Therefore, the timing of force application in fixed orthodontics should be planned accordingly.

CR in orthodontic pain management

Pain is characterized by the sensory and emotional component that shows individual variability. Orthodontic discomfort is primarily brought on by periapical tissue damage and a variety of biological reactions to orthodontic force. Undoubtedly, the sensation of pain associated with orthodontic treatment results from an immune response that alters blood flow after the application of orthodontic force. It is known that this causes a release of several chemical mediators, which causes a hyperalgesia reaction. With this evidence and a spike in levels of several neuropeptides produced, recent research has begun to elucidate the molecular basis of orthodontic pain. One of these mediators is the IL-1Beta, which controls bone remodeling in response to orthodontic force. These mediators' release has been demonstrated to adhere to circadian regularity.[21,22]

According to studies, pain sensation begins as soon as orthodontic force is applied, follows a curvilinear pattern, peaks after 24 h, and then begins to subside after 2–3 days. It then gradually lessens over a week. Orthodontic discomfort was found to vary throughout the day, with evenings and nights experiencing greater agony.[23]

Prescriptions for pre-emptive analgesics are indicated to treat any acute discomfort, followed by prescriptions for long-acting analgesics (such as etoricoxib, piroxicam, naproxen, or lumiracoxib), which may assist to lessen the inflammatory response brought on by orthodontic forces. Knowing that pain is generally worse in the morning and evening compared to the afternoon suggests that patients can be encouraged to take analgesics in accordance with this advice rather than needing to take them regularly, such as every 6 to 8 h.

Interestingly, significant diurnal changes are also present in the placebo effect, which can result in up to 40% of the pain threshold elevation. It was discovered that the pain threshold dramatically alters depending on the timing of the placebo administration.[24]

Clinical significance

- The goal of clinical management of orthodontic pain should be to time analgesic administration to coincide with the peak level of pain so that the greatest amount of analgesic blood levels are available to control the pain.
- Thus, by eliminating the conventional 6–8 hourly intake of analgesics, the understanding of diurnal fluctuations in pain might not only boost the effectiveness but also limit adverse effects.[21]
- In a trial performed on healthy subjects, pain threshold was seen to rise more quickly and significantly during the day when a placebo was labeled as an analgesic than it does at night. This highlights the importance of the timing of placebo administration in clinical practice.[24]

Influence of biomaterials on CR

Numerous recent investigations have shown a special function for CR-related genes in osseointegration controlled by titanium material surface characteristics. Ti4V6Al with dual-acid etching and the discrete crystalline deposition of hydroxyapatite nanoparticles significantly upregulated *Npas2*- a gene orthologous to CLOCK and downregulated the *PER1* gene, thus creating a microenvironment that mediated bone and implant bonding. For continued innovation and development of novel clinical techniques to be employed in dental and orthodontic implants, it is essential to have a complete grasp of circadian clock machinery from both the host and material aspects.[25,26]

Conclusion

The knowledge of circadian periodicity and its role in the field of orthodontics and dentofacial orthopedics is indispensable for a better understanding of the various physiologic and pathologic processes that could be encountered daily. This review would therefore serve as an overview, opening more avenues for further research on this topic that can greatly help the orthodontic fraternity.

Abbreviations	Full form
CR	Circadian rhythm
TTFL	Transcriptional–translational feedback loop
CLOCK	Circadian locomotor output cycles kaput
BMAL1	Brain and muscle aryl hydrocarbon receptor nuclear translocator 1
CRY 1,2	cryptochrome 1,2
PER1-3	period 1-3
DNA	Deoxyribose nucleic acid
mRNA	Messenger ribose nucleic acid
Rev- Erbα	Member of Nuclear receptor subfamily 1 group D
ROR	Retinoic acid-related orphan receptor
OPG	Osteoprotegerin
RUNX	Runt-related transcription factor
SOX9	SRY-box transcription factor
Wnt	Wingless integrated site
BMP	Bone morphogenic protein
Hh	Hedgehog
SMH	Skeletal mandibular hypoplasia
SAG	Hh signaling activator smoothened agonist
PDL	Periodontal ligament
COL1A1	Collagen type 1, alpha 1
RANKL	Receptor activator of nuclear factor kappa beta ligand
OTM	Orthodontic tooth movement
LSU activator	Louisiana State University
IL	Interleukin
Ti4V6Al	Titanium 4, vanadium 6 aluminum
Npas2-a gene	Neuronal PAS domain protein 2

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Conflicts of interest
There are no conflicts of interest.

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