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Review Article **Periodontics**

When Gums Follow the Clock-the Role of Oral Circadian Rhythm

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Abstract

Chrono-dentistry is a new area of study in dentistry that examines the relationship between circadian cycles and periodontal health. Circadian clocks are natural timekeeping mechanisms that synchronise daily cycles with physiological functions. Both the central nervous system and periodontal tissues, such as the gingiva, periodontal ligament, alveolar bone, and fibroblasts, express molecular clocks, which include genes like BMAL1(Brain and Muscle Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT) like protein), PERs (Period genes), Crys (Cryptochrome genes), and DEC1/2 (Differentiated Embryo Chondrocyte 1 and 2). With rhythmic gene expression influencing bone resorption, vascularization, and inflammation, these peripheral clocks regulate crucial processes such as tissue remodelling, wound healing, immunological responses, and cellular proliferation. A person's susceptibility to periodontitis is increased when their circadian cycles are disrupted by shift work, sleep deprivation, or genetic changes. This results in increased tissue degradation, heightened inflammatory mediators (Tumor necrosis factor-α, Interleukin-1β), and decreased salivary antioxidant capacity. CLOCK gene (Circadian Locomotor output Cycles Kaput) downregulation, particularly of BMAL1, enhances pro-inflammatory pathways controlled by NF-κB (Nuclear Factor κB), thereby accelerating bone loss and influencing bone resorption, vascularization, and inflammation. The potential of chronobiology-guided periodontal therapy is highlighted by our growing understanding of the molecular pathways relating circadian rhythm and periodontal disease. Long-term oral health may be supported and treatment outcomes may be enhanced by coordinating therapeutic and preventive measures with the circadian cycle.

Keywords: Chrono-dentistry, Periodontitis, Circadian Rhythm, Gene expression.

INTRODUCTION

The oral cavity has strong circadian (24-hour) clocks that regulate cellular processes in several tissues, including the gingiva, periodontal ligament, alveolar bone, and salivary glands. The fundamental components of the molecular clock (BMAL1, CLOCK, PERs, CRYs, and related regulators) exhibit rhythmic expression in periodontal cells and influence critical activities including inflammation, immune cell trafficking, tissue remodelling, and redox equilibrium [1].

According to recent preclinical and translational research, circadian disruption—caused by shift work, sleep disturbances, or genetic mutation of clock genes—modifies periodontal homeostasis and can worsen alveolar bone loss and periodontal inflammation. Mechanistically, BMAL1 deletion or downregulation causes the balance to shift in favour of NF-κB-driven cytokine production, oxidative stress, apoptosis, and increased inflammatory cell infiltration. This suggests a connection between periodontal damage and clock failure [2]. There are clinically significant links between systemic circadian health and oral disease, as evidenced by human and animal data showing that chronic periodontitis is linked to altered expression of circadian pathway genes in diseased mucosa and bone and that sleep duration and quality correlate with periodontal outcomes in epidemiologic and clinical studies [3].

These findings suggest the oral clock is both a mediator of periodontal physiology and a potential therapeutic target: timed (chronotherapeutic) interventions, modulation of sleep/circadian behaviors, or molecular targeting of clock-inflammatory crosstalk could complement conventional periodontal therapy. Nonetheless, important gaps remain — including human longitudinal evidence, tissue-specific clock dynamics in health vs disease, and clinical trials testing circadian-based interventions. Addressing these gaps will be essential to translate basic chronobiology into improved preventive and therapeutic strategies for periodontal disease [1].

Molecular Basis of Circadian Rhythms

Transcription-translation feedback loops (TTFLs), where activator and repressor proteins cycle with about 24-hour frequency, form the biochemical basis of circadian rhythms. Important mammalian elements like BMAL1 and CLOCK create a heterodimer that uses E-box elements to promote the production of downstream clock genes like PER and CRY. The negative feedback loop is closed when the PER/CRY complex builds up, moves to the nucleus, and suppresses BMAL1/CLOCK activity as explained in figure 1[4].

The oscillations' time and amplitude are adjusted by post-translational alterations such as phosphorylation (by CK1ε, for instance), ubiquitination, and regulated degradation of PER and CRY [5].

Beyond the TTFL, newly discovered elements like RUVBL2 draw attention to conserved but non-canonical clock regulatory modules and complicate the fundamental clock machinery [6].

Additionally, the molecular clock links cellular redox state, NAD^+ levels, chromatin remodelling, and circadian gene expression through interactions with metabolic and epigenetic pathways. This means that the oscillator not only maintains time but also incorporates physiological and environmental cues [7].

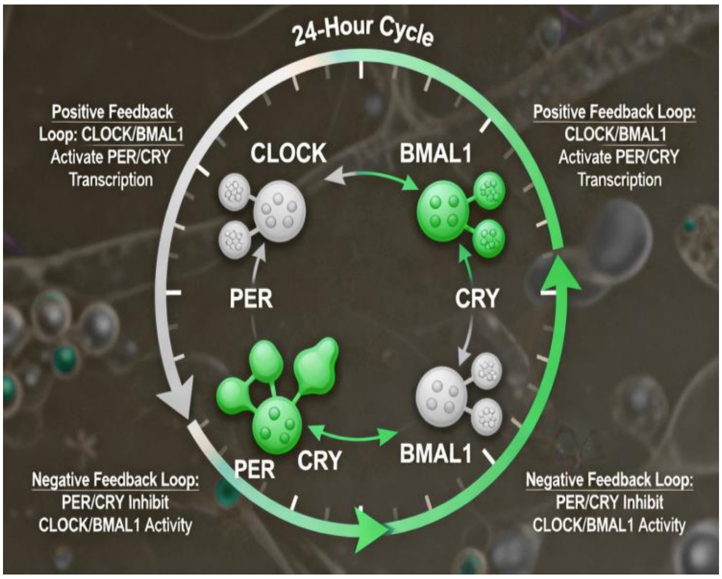

Figure 1: Molecular Basis of Circadian Rhythm

Oral Tissues and the Circadian Clock

Several oral tissues have independent circadian oscillators that directly affect tissue homeostasis; therefore, the oral cavity is not just a passive recipient of systemic rhythms. Ameloblasts (enamel forming cells) display rhythmic expression of core clock genes like BMAL1, CLOCK, PER1, and PER2, which regulate temporal patterns of gene expression, metabolism, matrix secretion, ion transport, and mineralisation during enamel formation, amelogenesis is controlled by the circadian clock. Ameloblast development, enamel matrix deposition, and mineralisation can all be hampered by circadian rhythm disruption, which may result in enamel abnormalities including hypoplasia. These rhythmic mechanisms highlight the crucial role of circadian biology in normal enamel development and are structurally mirrored by incremental growth lines in enamel (Retzius lines) [8].

In a more comprehensive review, Feng et al. explained how clock components (such as BMAL1, PER1/2, and CRY1/2) are rhythmically expressed in oral and maxillofacial tissues, such as salivary glands, tooth buds, and alveolar bone; consequently, the circadian clock can affect oral tissue development as well as maintenance and repair as explained in figure 2 [1].

For example, studies have demonstrated that the expression of aquaporin 5 (AQP5) in submandibular glands is driven by the central pacemaker (Suprachiasmatic nucleus, SCN) and exhibits strong daily oscillation [9].

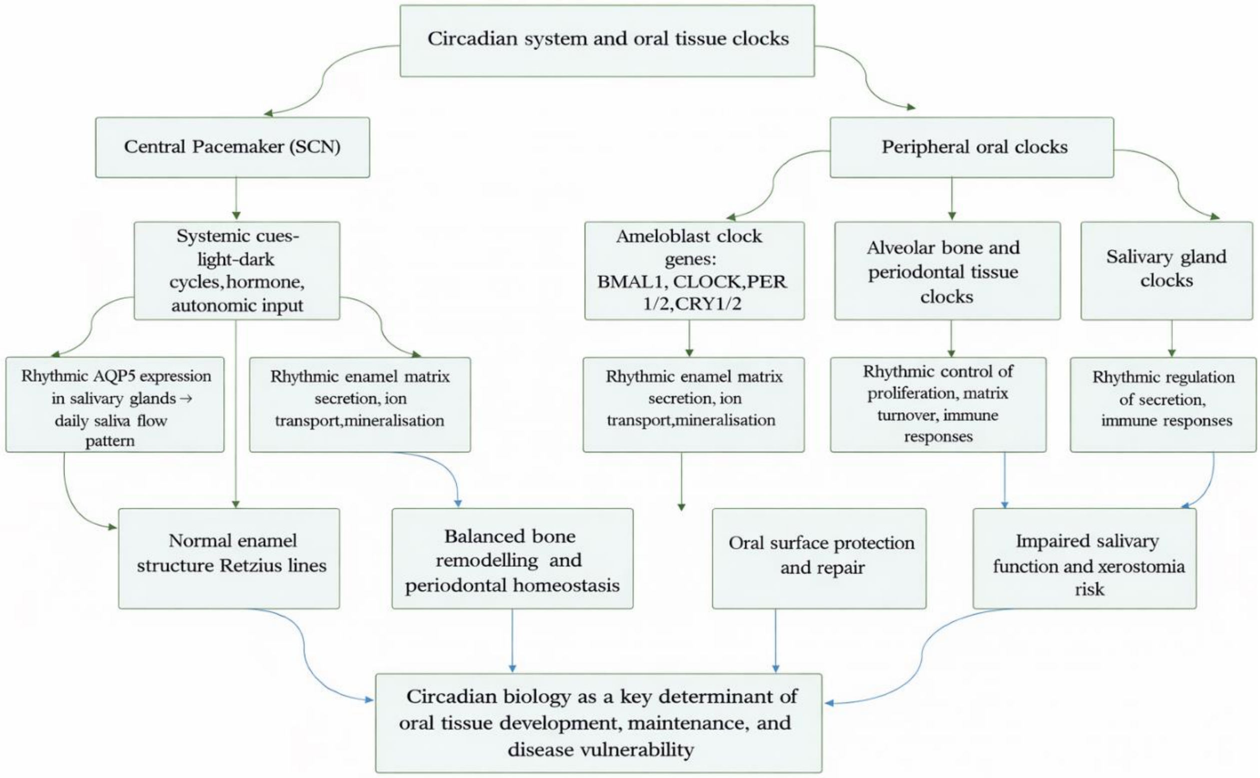

Figure 2: Oral tissues and Circadian clock

In order for tissues to optimise their activity according to the time of day (e.g., higher repair/turnover during rest phases), these tissue clocks are thought to mechanistically modify gene expression involved in proliferation, matrix production, ion transport, and metabolic flux. Because of this, circadian gene expression abnormalities caused by shift work, sleep disturbances, or genetic perturbations may reduce the ability of tissues to regenerate, make them more vulnerable to damage, and hasten degenerative processes. Therefore, taking into account circadian biology in oral tissues goes beyond simple systemic entrainment into a tissue-specific paradigm that may explain the pathophysiology of salivary glands, alveolar bone, and periodontal disease.

Circadian Rhythms in Oral Physiology

The orchestration of peripheral clocks in oral tissues and their synchronisation with systemic stimuli are reflected in the prominent 24-hour rhythms of mouth physiological activities. Unstimulated and stimulated submandibular saliva show statistically significant circadian variation in flow rates and concentrations of ions like sodium, potassium, and chloride (but not always proteins) across sampling times within 24 hours, making saliva flow and composition among the best-documented [10].Another study demonstrated that salivary secretory IgA (S-IgA) and cortisol follow daily rhythms; S-IgA peaks approximately 06:50 h whereas cortisol peaks around 09:04 h (in one small adult sample) — indicating time-of-day variation in oral immune protection [11].

Beyond saliva, there is growing evidence that gingival immune cell trafficking, periodontal ligament remodelling, and alveolar bone turnover all follow circadian patterns (though human data are more limited). Repair mechanisms (collagen synthesis, MMP activity) may preferentially take place during particular circadian phases, and the daily modification of immunological preparedness in the gingival sulcus probably influences sensitivity to microbial challenge throughout distinct phases of the day. These rhythmic processes suggest that the oral cavity is temporally optimised for function: night/rest phases promote tissue turnover, immunological monitoring, and repair, while day-active phases stress mechanical utilisation and clearance. Therefore, disruption of these cycles (e.g., sleep disturbance, irregular eating/chewing patterns) may impede healing, increase inflammation, and deteriorate homeostasis, laying the groundwork for disease processes.

Oral Clock and Disease Pathogenesis

There is growing interest in the function of circadian clocks in the pathophysiology of oral diseases. Genetic disruption of fundamental clock genes (including BMAL1) or exposure to circadian misalignment (light/dark changes, sleep disruption) has been shown in experimental animal research to increase inflammatory responses, hasten periodontal breakdown, and increase alveolar bone loss. After reviewing these events, Feng et al. propose that clock dysfunction increases osteoclast activation, macrophage dysregulation, reactive oxygen species buildup, and NF-κB signalling [1]. There is mounting epidemiologic evidence in human research that poor sleep, working shifts, and having an evening chronotype are linked to a higher incidence of periodontal disease and caries as explained in figure 3. This association may be mediated by disruption of salivary circadian rhythm, immunological defence, and microbial ecology. (Kurtović et al., narrative review on caries and chronotype) [12].

All of these findings point to the possibility that systemic or local circadian disruption can modify the pathophysiology of oral diseases by upsetting the equilibrium between host defence, tissue repair, and microbial assault. Thus, it might be appropriate to incorporate circadian health into periodontal risk assessment.

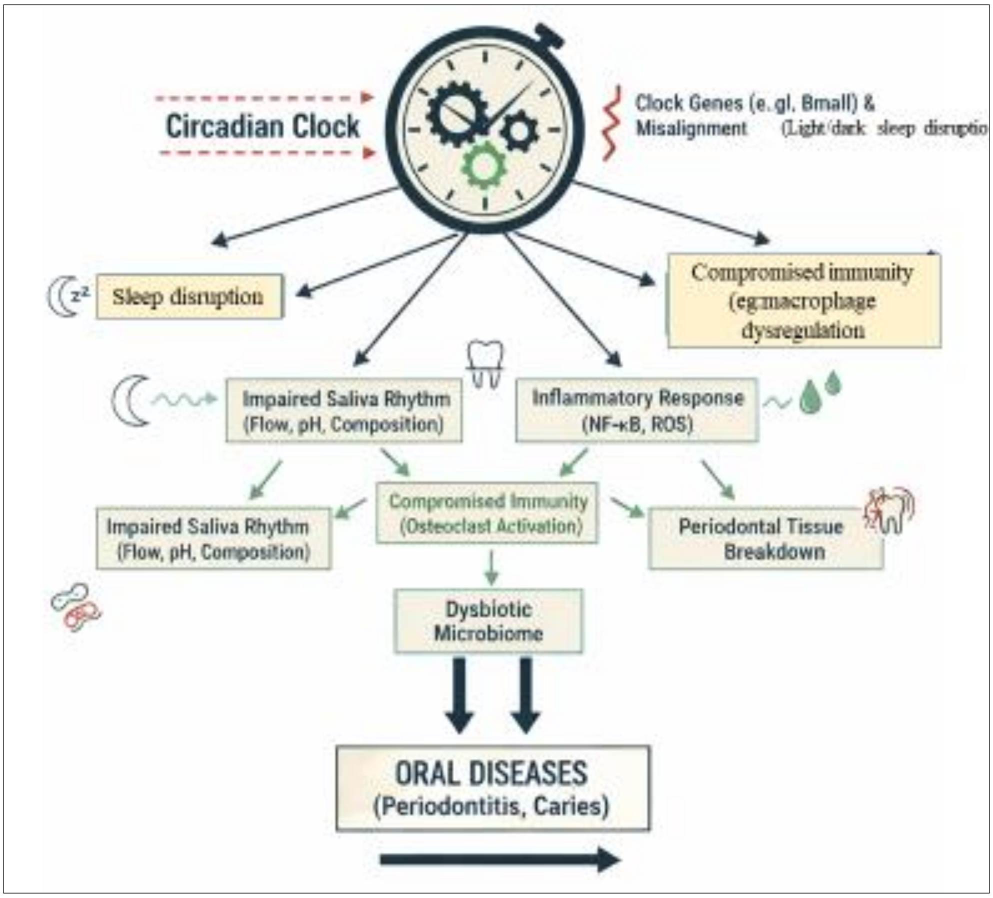

Figure 3: Oral Circadian Clock Disruption and Disease Pathogenesis

Chronotherapy in Dentistry

Aligning treatment interventions with biological time to maximise effectiveness and reduce negative effects is known as chronotherapy. This idea is still in its infancy but shows promise in dentistry. 24 papers (19 human, 5 animal) investigating time-of-day effects in dental healing, analgesia, and inflammation were found in a 2023 scoping review; despite their heterogeneity, the results show greater benefit when therapies are scheduled to coincide with peak tissue receptivity. In order to maximise efficacy and minimise negative effects, chronotherapy in dentistry entails scheduling dental procedures or medication delivery in accordance with the patient's circadian rhythms. For instance, variations in pain perception, salivary flow, and inflammatory response may make local anaesthesia, analgesics, or anti-inflammatory medications more effective at particular times of the day. Additionally, daily rhythms in cortisol levels, blood pressure, and healing capacity can be taken into account when scheduling operations like scaling, implant insertion, or periodontal therapy, improving patient comfort and treatment results [13].

A clinical editorial highlights the circadian regulation of processes like bone repair, immunological response, and nociception, implying that scheduled administration of antimicrobials and analgesics or morning or early-day surgical timing may improve result [14].

Oral Microbiome and Circadian Interaction

The oral microbiome itself exhibits circadian rhythms and reciprocally interacts with the host's circadian system, according to recent studies. Many dominant genera, such as Streptococcus, Prevotella, and Gemella, oscillated with ~24 h periodicity in a time-series 16S rRNA sequencing study of saliva in healthy adults (samples taken every 4 hours for three days); the functional gene content of the salivary microbiome also showed circadian patterns [15].

Circadian misalignment dramatically changed the relative abundance of dominant phyla/genera and disturbed functional pathways linked to immune/metabolic regulation in the oral microbiota, according to another controlled laboratory investigation conducted under forced desynchrony (e.g., 28 h "days") [16].

These results point to a reciprocal relationship: while microbial metabolites and signalling may feedback into host tissue clocks, influencing inflammation and repair, host circadian rhythms control microbial ecology through rhythms in salivary flow/composition, innate immune effectors, and nutrient availability. Circadian microbial–host synchronisation disturbances may promote dysbiosis, increase inflammation, and hinder tissue regeneration in the context of periodontal disease. Therefore, taking into account the timing of microbial challenge and temporal analysis of microbiome composition may give preventive and therapeutic oral microbiome techniques a new dimension.

Clinical Implications

There are various clinically significant ramifications to the developing circadian viewpoint in oral health, both for tissue physiology and microbial dynamics. First, while assessing periodontal and caries risk, doctors should take into account circadian risk factors (e.g., inadequate sleep, shift work, evening chronotype). Second, as many biomarkers (S-IgA, flow rate, ions) change over a 24-hour period, diagnostic approaches utilising saliva or gingival crevicular fluid should account for sample time [11]. Third, temporal optimisation may help with the scheduling of dental procedures and medication administration. For instance, antimicrobials should be administered when saliva flow and immune activity are at their peak, or morning treatments may be scheduled while the body is in repair mode. Fourth, as part of all-encompassing oral preventive care, patient education should incorporate circadian hygiene (regular sleep-wake schedules, timed eating/chewing cycles). Lastly, the connection between oral disease and circadian disruption emphasises the value of interdisciplinary cooperation (dentistry, sleep medicine, chronobiology) in the treatment of patients who are at risk. It is possible to improve results, customise treatment, and switch from reactive to time-aware preventive techniques by incorporating circadian health into dental practice.

Future Perspectives

Future study must methodically fill in a number of gaps in light of the growing body of information. To establish a connection between oral tissue clock gene expression, microbial cycles, and the clinical development of periodontal/carious disease, large-scale longitudinal human cohorts are required. In order to prove causation and give evidence for the creation of guidelines, interventional trials of chronotherapy in dentistry (timed surgery, time-targeted drug delivery) are required (currently noted as lacking in the scoping study) [13].

Dental regeneration and periodontal therapy may benefit from the discovery of small-molecule clock gene modulators or supplementary treatments like melatonin. Additionally, investigating the interactions between microbial rhythms, sleep timing, and feeding/chewing behaviours may result in chronobiome-modulation techniques for dysbiosis. In the end, incorporating circadian science into dentistry can move the discipline towards time-based oral health care by optimising both what and when to intervene.

CONCLUSION

Our knowledge of periodontal health and disease has been completely transformed by the revelation of circadian modulation inside dental tissues. The oral clock emphasises the importance of time in dental therapies by coordinating immune defense, microbial balance, and tissue regeneration. Chronodentistry, the application of chronobiology to dentistry, presents a new avenue for individualised, time-efficient therapies that improve prevention and repair. Future developments in clinical timing techniques and chrono-omics have the potential to redefine oral healthcare from a biological time perspective.

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