Exploratory Research and Hypothesis in Medicine **2023** vol. 8(2) | 143–149
DOI: 10.14218/ERHM.2022.00052

Review Article

The Influence of Dental Implants on the Circadian Clock and the Role of Melatonin in the Oral Cavity

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Received: April 26, 2022 | **Revised:** June 08, 2022 | **Accepted:** June 17, 2022 | **Published online:** June 29, 2022

Abstract

The circadian rhythm regulates many physiological human health and disease processes. The central circadian clock is located in the suprachiasmatic nucleus in the hypothalamus and controls a whole range of circadian clock genes. During bone remodeling, circadian rhythm gene expression was observed in osteoblasts and osteoclasts. Moreover, circadian rhythm genes are an essential part of the circadian network in the osseointegration of titanium implants. Namely, titanium biomaterials significantly affect the expression of the circadian clock gene in the oral cavity and thus regulate the establishment of osseointegration. In addition, vitamin D has potential practical implications for patients with dental implants because sufficient vitamin D levels before surgery improve the osseointegration process. Also, the hormone melatonin, whose production depending on the circadian rhythm, affects bone homeostasis. Therefore, melatonin affects bone formation and could serve as a regenerative agent by increasing the process of osseointegration. This review highlights the impact of dental implants on circadian rhythm and osseointegration.

Introduction

Osteointegration-based dental implants are generally accepted to treat complete and partial edentulism. Sound integration and maintenance of implants in the alveolar bone and the formation of new bone contribute to treatment success. However, the genetic background related to bone quality, vitamin D, melatonin, and peripheral circadian rhythm as elemental regulatory systems for establishing and maintaining osseointegration is very complex.[1] The circadian rhythm regulates many physiological processes of human health and disease.[2] There is growing evidence that the circadian clock could influence tooth development, salivary and oral epithelial homeostasis, and saliva production.[3] Circadian rhythm gene expression has been found in several epithelial craniofacial tissues, especially in basal cells of the oral epithelium, including the palatal and connective epithelium, and in epithelial remnants surrounding tooth roots. In addition, the saliva flow is known to follow a circadian rhythm.[4]

Bone mineralization in bone development is associated with circadian rhythm. Osteoblasts express circadian clock genes linked with the circadian signaling pathway. Also, the resorptive activity of osteoclasts shows circadian rhythmicity and is controlled by various endocrine hormones and cytokines. The circadian expression of many genes involved in phosphate and vitamin D metabolism regulation in the skeleton has been estimated by food intake.[5]

Central circadian clock components have an essential role during bone remodeling, a mechanism that strengthens the outcome of dental implants and preimplantation procedures such as bone augmentation.[5] The circadian clock is implicated in bone remodeling due to the regulation of homeostasis in mineralized tissue. Circadian rhythm genes are expressed in osteoblasts. Also, the resorptive activity of osteoclasts shows circadian periodicity and is maintained by numerous endocrine hormones.[5] It has been suggested that the circadian clock could affect enamel formation by stimulating amelogenin production. In addition to enamel, circadian rhythm is also essential in forming another hard tooth tissue, dentin.[6] During tooth development, the underlying circadian

Keywords: Circadian rhythm; Implants; Melatonin; Osseointegration; Titanium; Vitamin D.

Abbreviations: BMAL1 or ARNTL, brain, and muscle ARNTL-like protein; CCG, clock-controlled genes; CK1, casein kinase 1; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; HIF-1α, hypoxia-induced factor 1α; INF-γ, interferon-gamma; NF-κB, nuclear factor-kappa B; NPAS2, neuronal PAS domain protein 2; PER, period; REV-ERB, nuclear receptor subfamily 1 group D member 1; RANKL, receptor activator of nuclear factor kappa-B ligand; ROR, retinoic acid-related orphan receptor; RUNX2, runt-related transcription factor 2; SCN, suprachiasmatic nucleus; TNF-α, tumor necrosis factor-alpha.

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How to cite this article: Škrlec I. The Influence of Dental Implants on the Circadian Clock and Its Role of Melatonin in the Oral Cavity. *Explor Res Hypothesis Med* 2023;8(2):143–149. doi: 10.14218/ERHM.2022.00052.

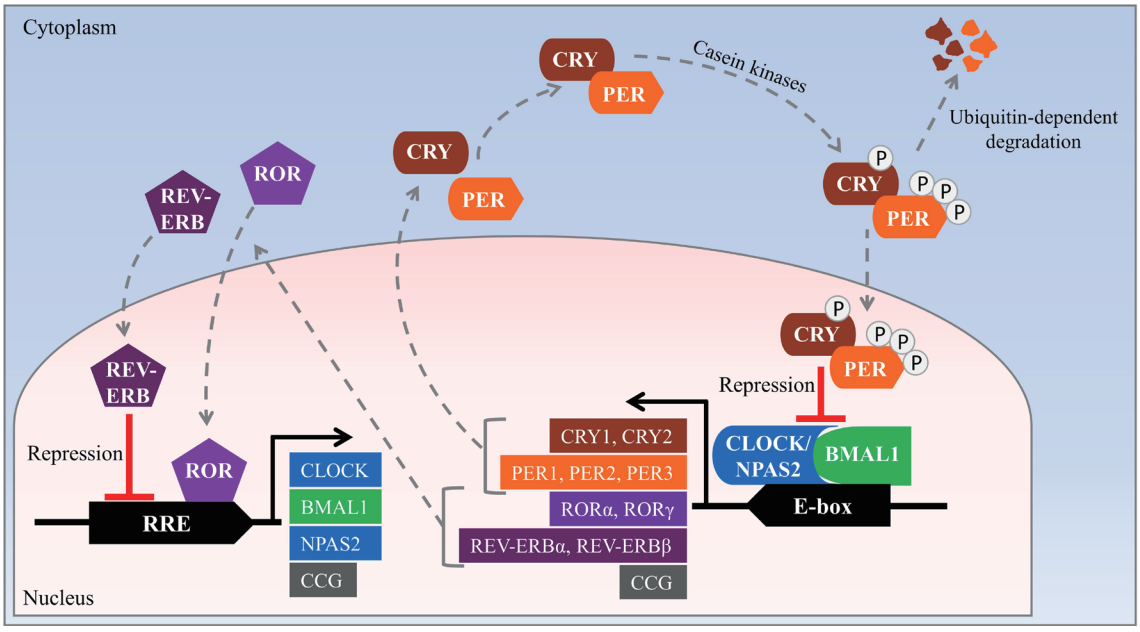

Fig. 1. The core clock mechanism of the circadian rhythm. BMAL1 and CLOCK trigger transcription of CRY and PER, nuclear receptors (REV-ERBs and RORs), and other clock-controlled genes (CGG). PER and CRY heterodimerize and phosphorylate by casein kinases and translate into the nucleus, where they inhibit the binding of the CLOCK(NPAS2):BMAL1 to the regulatory regions of target genes. In the second feedback loop, REV- ERBα inhibits the transcription of BMAL1 because it binds to the RORE element. In contrast, overnight, the same regulatory elements bind RORα and activate the transcription of BMAL1. Also, CLOCK(NPAS2):BMAL1 heterodimers induce the REV-ERBα and RORα expression. BMAL1, brain and muscle ARNTL-like protein 1; CCG, clock-controlled genes; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; NPAS2, neuronal PAS domain protein 2; PER, period; P, phosphate; RORα, retinoic-related orphan receptor alpha; RRE element, REV-ERB/ROR response element. Adapted according to Škrlec et al. 2020.[8]

rhythm components are active in both ameloblasts and odontoblasts during the bell phase.[7] Dentine development is marked by incremental lines for which a circadian motif has been noticed in mammals. Collagen production and secretion were detected in odontoblasts in a circadian manner, contributing to the periodicity of incremental lines in dentin. In addition, circadian rhythm gene polymorphisms could generate unique enamel morphology, thickness, and hardness. Therefore, circadian rhythm genes could be the target of further treatments with the possibility of hard tooth tissue regeneration.[6] An important marker in bone formation is osteocalcin. Osteocalcin is a component of the extracellular matrix of bone and is made by osteoblasts. Osteocalcin promoter activity is regulated in a circadian manner, and bone remodeling is accelerated at rest.[1,6] In addition to osteoblasts, osteoclasts are also crucial in bone remodeling. Further investigation to understand or decipher the circadian rhythm mechanism in bone remodeling could open up further opportunities for orthodontic medicine.[6]

Molecular basis of circadian rhythm

The core clock genes are expressed in circadian rhythmicity in the suprachiasmatic nucleus (SCN), and light is one of the main drivers of the central clock. The molecular basis of the circadian rhythm includes transcriptional and translocation feedback loops. The circadian rhythm is driven by the brain and muscle ARNTL-like protein 1 (BMAL1 or ARNTL) and circadian locomotor output cycles kaput (CLOCK) transcription factors. In contrast, transcription repressors are cryptochrome (CRY) and period (PER) transcription factors. The central transcription factors that make up the activation and positive part of the molecular clock are BMAL1 and CLOCK. The heterodimer CLOCK:BMAL1 enters the nucleus, where it initiates transcription by binding to a specific sequence, the E-box, in promoters of the target genes (Fig. 1).[8] CLOCK's main downstream goals include BMAL1 and its repressors, cryptochrome (CRY1, CRY2), period (PER1, PER2, and PER3), and multiple clock-controlled genes (CCG).[9] CRYs and PERs accumulate during the positive loop in the cytoplasm. They are controlled by casein kinase 1 (CK1) ε and CK1δ.[10,11] CK1ε and CK1δ phosphorylate PERs for degradation. If CK1ε phosphorylates heterodimer PER:CRY, it enters the nucleus and suppresses the CLOCK:BMAL1 heterodimer. As a result, CRYs and PERs suppress their own expression.[12,13] Posttranslational phosphorylation of CRYs and PERs promotes their degradation, which triggers a new circadian cycle, with increased CLOCK:BMAL1 heterodimer binding to the E-box of CCG.[8,14] Due to sequence similarity, neuronal PAS domain protein 2 (NPAS2) is orthologous to the CLOCK gene. NPAS2 constitutes a heterodimer with BMAL1 and triggers transcription of target genes. The heterodimer CLOCK:BMAL1 is essential for preserving circadian rhythm, and NPAS2 is a redundant transcription factor that acts as a reserve plan for CLOCK in peripheral tissues. In the lack of CLOCK, NPAS2 is a replacement for forming heterodimer NPAS2:BMAL1.[15]

The second circadian clock regulatory loop includes the retinoic acid-related orphan receptor (ROR) α and RORγ, and the REV-ERBα and REV-ERBβ genes. The CLOCK:BMAL1 heterodimer initiates their transcription by binding to the E-box elements of their promoters. RORs and REV-ERBs receptors bind to the ROR response element (RRE). REV-ERBα and β inhibit transcription, while RORα and γ stimulate the expression of target genes. RORs and REV-ERBs together create cyclic fluctuations in the expression of many CCG, including the regulation of BMAL1 transcription.[8,10] REV-ERBα accumulates rapidly and prevents BMAL1

Table 1. Association of circadian rhythm genes with dental tissues

Gene	Gene function in dental tissues	References
BMAL1	Production in ameloblasts	Zheng et al. 2013[19]
	Production during tooth development	Zheng et al. 2011[20]
	Overexpression associated with enamel morphology, thickness, and hardness	Zheng et al. 2013[19]
	Stimulates amelogenin production	Zheng et al. 2013[19]
CLOCK	Production in ameloblasts	Zheng et al. 2013[19]
	Production during tooth development	Zheng et al. 2011[20]
NPAS2	Important for osseointegration	Morinaga et al. 2019[18]
PER1	Modulation by titanium in bone marrow stromal cells	Hassan et al. 2017[21]
	Production in ameloblasts	Zheng et al. 2013[19]
	Production during tooth development	Zheng et al. 2011[20]
PER2	Production in ameloblasts	Zheng et al. 2013[19]
	Production during tooth development	Zheng et al. 2011[20]
	Production in odontoblasts	Zheng et al. 2011[20]

BMAL, brain and muscle ARNTL-like; CLOCK, circadian locomotor output cycles kaput; NPAS2, neuronal PAS domain protein 2; PER1, period 1.

transcription, while RORα accumulates more slowly and promotes BMAL1 transcription. In this way, the stability and robustness of the rhythmicity of the internal clock system are enhanced.[16] In addition, the transcriptional and translational feedback loop creates rhythms in the expression and levels of downstream CCG.[10] All of these connected feedback loops create a circadian rhythm.

Circadian rhythm in osseointegration

The term osseointegration was first used to explain histological remarks that bone and bone marrow tissues show a tight connection with the surface of the endosseous titanium-based implant element without the formation of fibrous tissue.[17] Cell culture approaches and animal models were utilized to characterize bone formation patterns on the implant surface.[1] Titanium-containing biomaterial is often used in implantology for dental implants.[6] Dental implants consist of an endosseous anchoring piece and transmucosal support that sustains different dentures. The benefit of a dental implant relies on the biological reactions to xenobiotic materials and the endosseous implant placement in the mandible. Furthermore, in acquiring a sound bone-implant connection without clinical symptoms and signs of inflammation or infection, osseointegration plays a crucial role in permanent implant immobility.[1]

Circadian rhythm has a vital function in cell differentiation. Mesenchymal stem cells are adult stem cells with multipotent ability to differentiate and could be isolated from tooth tissue, bone marrow, amniotic fluid, adipose tissue, and additional sources.[15] The expression profile of genes linked with osteogenic mesenchymal stem cell differentiation shows that molecular circadian rhythm regulates mesenchymal stem cell differentiation. Circadian clock transcription factors control the expression of core clock genes and other clock-controlled genes (CCG). Tissue-specific differentiation of mesenchymal stem cells could be affected by clock gene expression via CCG. The positioning of titanium implants creates a distinct cellular condition that could increase the osteogenic differentiation of bone marrow mesenchymal stem cells.[15] Thus, PER1 gene expression is reduced in stromal bone marrow cells due to titanium-based biomaterials, essential for osseointegration.[6]

Furthermore, mesenchymal stem cells susceptible to various titanium substances in vitro improved osteogenic differentiation.[15] Almost 30% of genes show circadian oscillations,[1,18] and among them in the maxillo-mandibular complex is osteocalcin. Although the peripheral bone circadian clock function has not been thoroughly investigated, implant-induced microenvironmental change significantly affects NPAS2 and PER2 gene expression regulation or dysregulation in peri-implant tissue (Table 1).[18–21] It might contribute a new hint to understanding the process of osseointegration.[1]

The role of BMAL1, CLOCK and NPAS2 in osseointegration

Successful dental implants require establishing a solid connection with bone tissue. Nonetheless, the clarification of how biological systems achieve osseointegration is, until now, insufficient.[22] The circadian clock can affect bone absorption by regulating bone energy metabolism.[23] BMAL1 plays a vital role in regulating bone absorption and formation and is a crucial component of the molecular circadian clock.[19,24] Mutations in the BMAL1 gene in mice lead to ectopic calcification and abnormal cartilage reendothelialization,[25] whereas bone density is reduced in mice with the CLOCK gene mutation. Overexpression of the BMAL1 and CLOCK genes inhibits the expression of the receptor activator of the nuclear factor kappa-B ligand (RANKL) gene.[26] BMAL1 delays bone resorption and its expression inhibits NF-κB. The interaction of BMAL1 and NF-κB itself is significant during inflammatory processes because NF-κB mediates the activation of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[27] Various studies have shown that the placement of titanium implants has the most significant effect on circadian rhythm gene expression.[28] NPAS2 and BMAL1 gene expression increased, while PER2 expression decreased. Biomaterials made of titanium with complex surfaces have a more significant effect on expressing distinctive circadian clock genes than untreated surfaces.[28] Titanium implants with complex surfaces alter CCGs expression near the implant so that NPAS2 becomes a partner tran-

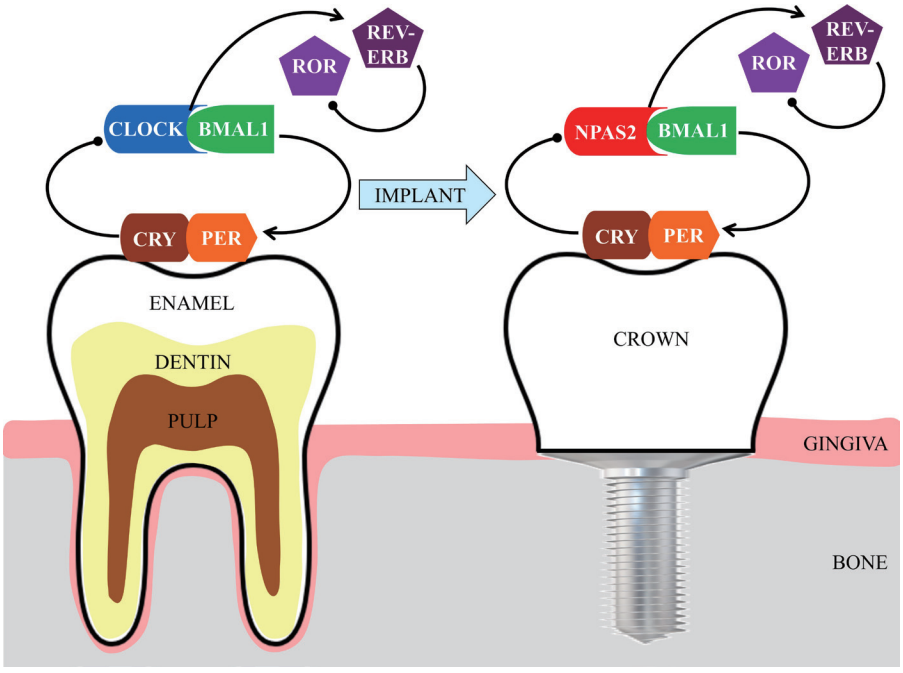

Fig. 2. The transition from CLOCK to NPAS2 after titanium implant placement. There is a change in clock-controlled gene expression near titanium implants – NPAS2 becomes a transcription partner with BMAL1. It stimulates the synthesis of proteins that promote bone and implant binding in the process of osseointegration. BAML1, brain, and muscle ARNTL-like protein 1; CLOCK, circadian locomotor output cycles kaput; neuronal PAS domain protein 2; CRY, cryptochrome; PER, period 1; REV-ERB, nuclear receptor subfamily 1 group D member 1; ROR, retinoic acid-related orphan receptor.

scription factor with BMAL1 in the NPAS2:BMAL1 heterodimer (Fig. 2). Based on this, it can be seen that NPAS2 is the preferred molecular counterpart of BMAL1 in the existence of titanium implants.[18] The CLOCK:BMAL1 heterodimer and NPAS2:BMAL1 heterodimer trigger various groups of genes.[29] The circadian rhythm regulates many CCGs, and the transition from CLOCK to NPAS2 after titanium biomaterial implantation modifies CCG expression, including proteins that promote bone and implant binding.[15,30] The expression of NPAS2 in interface tissue could therefore be the basis of osseointegration.[15]

The surface of titanium biomaterials is subject to oxidation, and the microenvironment around titanium biomaterials is hypoxic. Therefore, there is an increase in the signaling of hypoxia-induced factor (HIF)-1α in mesenchymal stem cells exposed to titanium biomaterials.[15,31] A hypoxic or xenobiotic microenvironment can facilitate molecular sensors that contain the PAS domain. BMAL1 is such a PAS detector for hypoxic or xenobiotic cell response. BMAL1 dimerizes with hypoxia-induced factors and thus triggers HIF-1α for chondrogenic differentiation.[1,18] Therefore, it is hypothesized that implantation of titanium materials could cause numerous consequences on mesenchymal stem cells expressing NPAS2, leading to regulation and raised binding activity of NPAS2 to DNA.[32]

The microenvironment produced by titanium biomaterials prefers the role of NPAS2, which can trigger the cooperative expression of CCGs that mediate bone and implant binding.[15] The function of NPAS2 determines the molecular mechanism of osseointegration. NPAS2 in peri-implant tissue is vital in establishing osseointegration[18] because it directly regulates collagen expression.[1]

The function of CRY and PER in osseointegration

Studies have shown that CRY2 and PER2 are essential in regulating bone volume.[19,20] Thus, CRY2 acts on osteoclasts, while PER2 affects osteoblasts.[19,26] Mutations in mice's CRY and PER genes led to increased osteoblast activity and bone mass.[33,34] In addition to acting on osteoclasts, CRY2 is also crucial for the stability of the extracellular cartilage matrix. PER2 is vital for bone maturation, and the PER2 mutation promotes osteoblast proliferative activity.[26] In combination with melatonin, PER2 plays a crucial role in modulating bone growth.[35] CRY2 and PER2 affect bone mass and bone volume through osteoclasts and cell differentiation.[6]

Titanium biomaterials change the expression of circadian rhythm genes by increasing the expression of NPAS2 and decreasing the expression of PER1 and PER2 genes.[3,15]

The impact of vitamin D on osseointegration

Vitamin D is a critical component in bone metabolism and is vital for calcium metabolism and the regulation of phosphorus and calcium homeostasis.[36] Due to its anti-inflammatory properties, vitamin D benefits oral health as it increases bone mineral density and reduces bone resorption.[37] Vitamin D deficiency harms new bone formation and bone contact with the implant. Patients with low vitamin D levels are more prone to dental implant failure.[38]

Circadian clock and extracellular cartilage matrix may establish vitamin D-regulated osteointegration. Vitamin D insufficiency negatively impacts osseointegration, resulting in a loss of bone and implant integration.[39] NPAS2 and BMAL1 are overregulated around implants, reducing their expression by vitamin D insufficiency. NPAS2 is expressed in the extracellular cartilage matrix, and vitamin D deficit does not influence the extracellular cartilage matrix gene expression around the implant. Peripheral circadian rhythm is required to establish osseointegration, which

triggers the production of a specified group of cartilage matrix proteins that could integrate the implant surface and bone tissue.[22] Vitamin D deficiency interferes with the osseointegration of titanium biomaterials.[40] Therefore, implant failure may occur during early surgery due to osseointegration failure during the injury recovery phase or after the implant has been used for some time.[21]

Systemic administration of vitamin D before dental implant placement surgery may benefit patients.[37] Vitamin D supplementation improves osseointegration in animals with systemic diseases and is similar in humans because vitamin D enhances the osseointegration process.[38] It was observed that higher vitamin D levels measured on the day of surgery were associated with better radiologically assessed osseointegration of implants.[41]

When osseointegration is failed, restorative alternatives are restricted to surgical removal of the implant. Therefore, satisfactory serum vitamin D levels are a required criterion for the curative success of titanium implants.[21] Vitamin D deficiency has mostly affected NPAS2,[1] essential for implant integration.

Melatonin effects on osseointegration

Bone remodeling includes cytokines, growth factors, hormones, and other molecules, with melatonin modulating bone formation and absorption.[42] Melatonin is a hormone produced in the pineal gland and positively regulates bone formation and homeostasis.[43,44] Melatonin levels in saliva show a circadian rhythm with the highest values during the night,[45] and the hypothalamus influences its production.[42] In the oral cavity, melatonin may play a role in maintaining and regenerating alveolar periodontal and peri-implant bone.[43] In addition, it has anti-inflammatory and antioxidant effects as it destroys reactive oxygen species.[42,45,46] Melatonin stimulates the differentiation of mesenchymal stem cells into osteoblasts and promotes bone formation.[43,47] It also enhances type I collagen synthesis and increases bone sialoprotein expression.[43,45] Melatonin can affect the release of several factors that affect bone, such as calcitonin, corticosterone, growth factors, and immune factors, and is an essential modulator of calcium and phosphorus metabolism.[43] Beneficial effects of melatonin in bone regeneration near titanium dental implants have been observed, whether applied topically to implant bearings, coated the implant, or injected near the implant at the time of positioning.[42,48] Melatonin may play a role in all bone repair phases (inflammatory, proliferative, and remodeling) due to its regulatory effects on inflammation, antioxidant properties, bone cell regulation, and collagen synthesis and deposition stimulation.[49] In addition, melatonin increases the number of blood vessels, a prerequisite for supplying mineral elements and migrating angiogenic and osteogenic cells.[50] Consequently, histological evaluation of the peri-implant bone shows more trabecular bone but less cortical bone and more significant bone contact with the implant in melatonin-treated sockets than untreated.[51,52] The use of melatonin for osseointegration may be of interest because it promotes bone growth when used in combination with dental implants.[43]

Melatonin increases the expression of runt-related transcription factor 2 (RUNX2), which induces the expression of osteogenic genes, including bone morphogenetic proteins and osteocalcin, thereby accelerating the synthesis and mineralization of new bone.[35,53] Melatonin is a significant regulator of osteoblast differentiation.[54] By increasing the expression of the RUNX2 gene and osteocalcin, melatonin reduces osteoblast apoptosis caused by oxidative stress.[55] In addition, melatonin may attenuate pro-inflammatory cytokines such as TNF-α, IL-12, INF-γ, IL-1β, and IL-6, while stimulating the production of the anti-inflammatory mediator IL-10.[35,53] Melatonin regulates osteoclastogenesis, oxidative stress, and autophagy by activating NF-κB, thereby reducing pro-inflammatory cytokine levels (TNF-α, IL-1β, and IL-6).[56,57] Moreover, melatonin can prevent peri-implantitis by inhibiting the NF-κB signaling pathway and reducing RANKL protein levels. In contrast, melatonin promotes proliferation, mineralized matrix formation, alkaline phosphatase activity, and osteogenic gene expression.[56]

The direct connection between circadian rhythm and melatonin is the binding of melatonin to ROR,[58] which stimulates the synthesis of BMAL1 and NPAS2 genes, which play an essential role in the osseointegration of dental implants.[15] In addition, BMAL1 inhibits the NF-κB signaling pathway that mediates the pro-inflammatory response, whereas melatonin has the opposite effect on NF-κB. The antioxidant and anti-inflammatory properties of melatonin limit the formation of free radicals and bone resorption after implant placement.[58] Dental implant coatings with melatonin increase the expression of the RUNX2 gene, bone morphogenetic proteins, and osteocalcin, necessary for osteoblast function and bone mineralization.[53,59] The local administration of melatonin is more effective than its systemic administration, increases calcium deposition around implants, and accelerates osseointegration around titanium implants.[53,55]

Future directions

Circadian rhythm adapts to the physiological functions of the individual daily, including the process of osseointegration. Biomaterials in the oral cavity directly affect the peripheral circadian rhythm. Therefore, by modifying the components of the peripheral clock, we can improve the process of osseointegration. NPAS2 is the most significant shift in peripheral circadian rhythm after implant placement that contributes to osseointegration. In addition, vitamin D and melatonin supplements are straightforward methods to improve the osseointegration of dental implants. Thus, vitamin D enhances the osseointegration of titanium implants and cellular healing processes.[21] In contrast, the topical application of melatonin at implant positioning may facilitate a more significant bone connection with the implant, thus promoting osteointegration.[42] Melatonin is available in various forms, from sublingual tablets, oral sprays, toothpaste, mouthwashes, and pharmaceutical gels.[45] Understanding the molecular processes involved in osseointegration requires additional research to assess the impact of different biomaterials on circadian rhythm in the oral cavity. This is especially important in today's era of personalized medicine when knowledge of an individual's circadian rhythm, determined based on chronotype through validated questionnaires, can be significant for treatment and could be included as an essential component of preoperative prediction for dental implant treatments.

Conclusion

An increasing body of evidence demonstrates the significance of peripheral circadian rhythms in osseointegration. The most crucial change in peripheral circadian rhythm during osseointegration is NPAS2 which might be the basis for developing treatment approaches created to enhance osseointegration or re-establish the integration of implants and bone. In addition to the molecular basis, osseointegration is also influenced by vitamin D and melatonin. Satisfactory serum vitamin D levels before surgery and

topical application of melatonin after implantation promote the production of new bone and increase bone thickness near titanium dental implants. Therefore, this approach to the osseointegration of titanium implants could help in new therapeutic strategies for dental implant treatments.

Acknowledgments

None.

Funding

This work was partly supported by a grant from the Croatian Ministry of Science and Education and dedicated to multi-year institutional financing of scientific activity at the Josip Juraj Strossmayer University of Osijek, Faculty of Dental Medicine, and Health, Osijek, Croatia (IP6-FDMZ-2021).

Conflict of interest

IŠ has been an editorial board member of *Exploratory Research and Hypothesis in Medicine* since November 2021. The author has no other conflict of interest to report..

Author contributions

I.Š. conceived of the subject content for this manuscript, researched and analyzed the literature, originally designed and created the figures, and wrote the entire manuscript.

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