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Research Article

Melatonin as a Modulator of Osseointegration: Mechanisms, Evidence and Clinical Potential in Implant Dentistry

[1]Georgia Petraki, [1]Sofia Stefania Boutiou, [1]Androniki Athanasiou, [1]Angelos Sfyrakis Velivasakis, [2]Panagiotis Kafas, [3]Mohammed Al Khawalde, [2]Theodoros Lillis and [2]Nikolaos Dabarakis

[1]Dental Students, School of Dentistry, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece
[2]Department of Oral Surgery and Radiology, School of Dentistry, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece
[3]Consultant of Oral and Maxillofacial Surgeon, King Hussain Medical, Amman, Jordan

Abstract

Osseointegration, the biological integration of dental implants with bone, is critical for the long-term success of implant-supported restorations. Despite advances in implant materials and techniques, achieving rapid and reliable bone healing remains a challenge. Melatonin, a biologically active molecule with antioxidant, anti-inflammatory and immunomodulatory properties, has shown potential to enhance bone regeneration and implant stability. This study aims to evaluate the role of melatonin in promoting osseointegration and to explore its potential clinical applications in implant dentistry. A narrative review of laboratory, animal and preliminary clinical studies investigating the effects of melatonin on bone healing and implant stability was conducted. Studies were selected based on the use of melatonin in local application, systemic supplementation or incorporation into implant surfaces. Key outcomes assessed included osteoblast activity, osteoclast inhibition, vascularization, bone density and healing time. Laboratory and animal studies demonstrated that melatonin enhances osteoblast proliferation, reduces osteoclast-mediated bone resorption and promotes vascularization through the regulation of vascular endothelial growth factor. Preliminary clinical studies indicated improved bone density on radiographic assessment and reduced healing time following local melatonin application. However, evidence remains limited and heterogeneity in dosing, administration methods and follow-up periods was observed. Melatonin shows promising potential to enhance osseointegration and accelerate bone healing in dental implant procedures. While initial findings are encouraging, optimal dosing, delivery methods and long-term safety remain unclear. Well-designed, controlled clinical trials are necessary before melatonin can be recommended as a standard adjunct in implant dentistry.

Key words: Osseointegration, dental implants, melatonin, bone healing, osteoblast, osteoclast, vascularization, implant stability

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Corresponding Author: Panagiotis Kafas, Department of Oral Surgery and Radiology, Faculty of Health Sciences, School of Dentistry, Aristotle University of Thessaloniki, Greece

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INTRODUCTION

The successful completion of dental implant surgery is dependent on osseointegration or the process by which bone becomes directly structurally and functionally related to the implant surface. Osseointegration provides stability for the implant to be used for mastication[1-3]. Surgical approach, type of implant and quality of bone in the implant site are all factors that influence osseointegration; however, greater focus has been placed on the possible use of biological approaches to enhance osseointegration as a result or outcome. One biological approach that is of interest is melatonin, which is a hormone that regulates sleep[4,5]. Not only does melatonin have effects on circadian rhythms, but it has been shown to interact with systems that regulate inflammation and immune function and positively impact bone[6,7]. Melatonin is gaining greater interest in the field and there is potential it may support or enhance the integration of bone and dental implants[8-11]. Melatonin promotes osteoblast differentiation and increases matrix protein production, which may accelerate peri-implant bone formation[10,11].

This study compiles the available experimental and clinical literature to better understand the pathways that lead to osseointegration as a result of melatonin supplementation. The study also highlights the trends identified in the available literature, as well as some areas that may require additional clinical support and relevance related to future implant-related research.

MATERIALS AND METHODS

The studies chosen for this review were based solely on peer-reviewed journal articles found using PubMed/MEDLINE, Scopus and Google Scholar search engines. These searches included articles published between 1999 and 2025, which are considered to represent the years during which experimental and clinical studies on the effect of melatonin on bone biology and the process of osseointegration of dental implants were conducted. Articles that contained only English-language material and were the result of direct experimental or clinical work were considered acceptable. Thus, the scope of this review was limited to experimental, animal and human studies related to the biological mechanisms, the effects of melatonin on healing and the influence of melatonin on clinical care regarding dental implant osseointegration. Studies that did not investigate the biological properties, per se, of the peri-implant bone biology were eliminated from this review.

Articles that included any biological effect of melatonin on the bone healing process, how implants become integrated with bone and how melatonin generally affects the tissues surrounding dental implants (peri-implant tissue) were considered for inclusion as potential criteria for eligibility. All types of studies (i.e., *in vitro*, animal and clinical studies) were included to create a comprehensive amount of available published information.

Articles were excluded if they did not report outcomes relevant to dental implants or peri-implant bone healing, focused exclusively on circadian rhythm or sleep without providing insights relevant to bone or immune function or were not primary experimental or clinical studies.

Studies describing melatonin's biological, immunomodulatory or anti-inflammatory effects were included when these findings could provide insights into potential mechanisms involved in implant osseointegration.

A narrative review was chosen to collect the literature related to melatonin and implant osseointegration due to the large quantity of heterogeneity relative to design and experimental models, entry routes, dosing schedules and outcome measures. Due to these variances, a quantitative analysis could not be performed, as no uniform methodology was available for systematic review or meta-analysis. A narrative design permits a complete and integrated assessment of the available evidence and preliminary clinical data. Therefore, the interpretation of facts relating to the context of the evidence highlights knowledge gaps for consideration when performing subsequent research.

The 35 citations listed were collected because they represent essentially all of the directly relevant experimental and clinical evidence available in the specified electronic databases on melatonin's biological and clinical effects on bone healing in the topic of dental implants.

MECHANISM OF ACTION

Melatonin is naturally produced by the human body, mainly by the pineal gland[4]. Melatonin can also be produced in smaller amounts from a few other sites in the body including the gastrointestinal system and bone marrow[10]. Melatonin is primarily produced during the night and this is important because it regulates the rhythm of sleeping and waking; however, the roles of melatonin go far beyond sleep regulation[4,10]. Melatonin has antioxidant and anti-inflammatory properties; it quenches free radicals and activates enzyme pathways to protect the cell from reactive oxidative stress[5,11-13]. On the immune side, melatonin can modulate the body's subsequent responses to injury or inflammation and contributes to regulating key signaling molecules[6,13]. The more general impact of melatonin in organic systems introduces emerging opportunities for this substance in aspects of bone repair and implant dentistry[9].

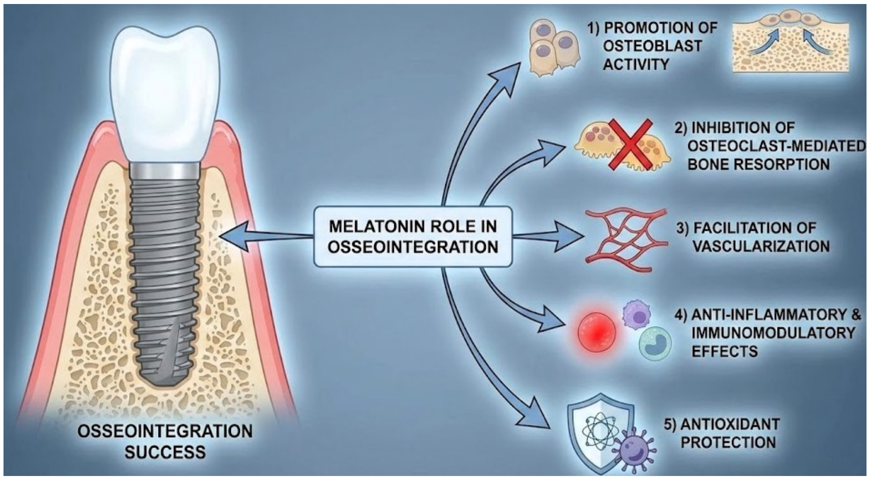

Fig. 1: Pleiotropic effects of melatonin on the process of dental implant osseointegration (Image AI designed)
This schematic illustrates the five primary biological pathways through which melatonin enhances the stability and integration of dental implants

BONE HEALING AND OSSEOINTEGRATION

The biological process of bone healing after an implant is placed is complex and not rapid. It unfolds in phases:

- Inflammation begins immediately following implant placement[14,15]
- Vascularization (the growth of blood vessels into the site) takes place
- Stem cells arrive at the location and begin differentiating into bone-forming cells[16]
- Precursor cells lay down a new bone matrix, which begins mineralization[17,18]

The goal of these stages is to form an intimate connection between the bone and the implant. That union is referred to as osseointegration, which is a stable surface bond without interposed fibrous tissue[2,17]. The faster the process unfolds, the better the quality of implantation. This is a place where biological enhancers like melatonin can make a real difference[3,8] (Fig. 1, Table 1).

WHAT MIGHT MELATONIN CONTRIBUTE TO BONE INTEGRATION?

Supporting osteoblast activity: Melatonin appears to promote the growth and activity of osteoblasts, the bone-forming cells[19]. In laboratory-based work with cell lines and isolated cells, when osteoblasts were exposed to melatonin, they produced increased amounts of proteins and enzymes that are required to form bone, alkaline phosphatase, type I collagen and osteocalcin[20]. There are also indications that melatonin promotes faster maturation of these cells, indicating quicker development of bone around the implant location[19,20].

Decreasing bone resorption: At the same time, melatonin seems to modulate osteoclast activity, i.e., the cells responsible for bone resorption, via signaling through pathways like RANKL and OPG, two key components that are involved in bone resorption[21,22]. By shifting this balance, melatonin may help maintain newly formed bone at the implant insertion site.

Facilitating vascularization: Healing tissue requires both oxygen and nourishment, so the need for a blood supply is vital. Melatonin appears to aid the maintenance of the blood stream level of Vascular Endothelial Growth Factor (VEGF), i.e., a growth factor known for stimulating new blood supply formation. Therefore, a better blood supply with melatonin could help to promote early healing and long-term healthy bone[23,24].

Limiting inflammation: While some inflammation occurs typically at a healing location, excessive or prolonged inflammation can restrict osseointegration. It appears that melatonin modifies immune function at the healing location[6,25]. For one, it promotes macrophages to take on an anti-inflammatory role of repair[13,25]. This process may help facilitate a transition or later stage of repair from inflammation into regeneration[13,26].

Table 1: Overview of melatonin's role in osseointegration: Actions, evidence, applications, benefits and limitations

Section (References)	Key points
Melatonin's biological actions (Cutando *et al.*[4], Reiter *et al.*[5], Sanidhya *et al.*[6], Tresguerres *et al.*[10], Gómez-Moreno *et al.*[11], Hardeland[12] and Srinivasan *et al.*[13])	**Antioxidant:** Protects healing tissue from oxidative stress **Anti-inflammatory:** Limits prolonged inflammation and modulates cytokines **Immunomodulatory:** Shifts macrophages toward a repair phenotype **Pro-angiogenic:** Enhances VEGF expression and vascular growth **Osteogenic:** Increases osteoblast differentiation and collagen synthesis **Anti-resorptive:** Reduces osteoclast activity through RANKL/OPG balance
Evidence summary (Ahmadpour *et al.*[8], Roth *et al.*[19], Dalla-Costa *et al.*[20] and López-Valverde *et al.*[32])	***In vitro*:** Increased osteoblast survival and matrix protein production **Animal studies:** Greater bone-implant contact and mechanical stability **Clinical studies:** Improved bone density and faster healing, though limited sample sizes
Methods of application (Ahmadpour *et al.*[8], Yi *et al.*[29], Wu *et al.*[30], Hazzaa *et al.*[31], López-Valverde *et al.*[32] and Ravella *et al.*[33])	**Local:** Gel or powder applied directly to implant site **Systemic:** Oral supplementation; non-targeted effect **Implant surface coating:** Gradual release from titanium coating
Potential benefits (Cutando *et al.*[4], Reiter *et al.*[5], Sanidhya *et al.*[6], Tresguerres *et al.*[10], Gómez-Moreno *et al.*[11], Hardeland[12] and Srinivasan *et al.*[13])	Naturally produced and biocompatible Encourages bone formation and limits inflammation Low cost compared to other biologic enhancers
Current limitations (Cutando *et al.*[4], Reiter *et al.*[5], Sanidhya *et al.*[6], Ahmadpour *et al.*[8], Ismail *et al.*[27], Kiran *et al.*[28], Wu *et al.*[30], Hazzaa *et al.*[31] and López-Valverde *et al.*[32])	Optimal dosage and method of delivery remain uncertain Local bioavailability and release kinetics not well defined Limited long-term human data
Future directions (Tresguerres *et al.*[10], Gómez-Moreno *et al.*[11], Hardeland[12], Srinivasan *et al.*[13] and Wang and Yeung[14])	Evaluate combined use with other bone-promoting agents Develop responsive coatings for controlled melatonin release Conduct large clinical trials in high-risk groups (diabetics, smokers, elderly)

Antioxidant for oxidative stress: After implant surgery, generally (especially for individuals with systemic issues such as diabetes or a history of smoking), implant sites may be influenced by oxidative stress. It may be possible to diminish oxidative damage with the antioxidant benefit provided by melatonin, protecting the recovery cells, healing tissue and bone formation cells[12,27,28].

WHAT THE RESEARCH SHOWS?

Animal studies: In animal models, specifically rodents (rats), melatonin has been delivered directly to the surgical site (either by way of gel or powder) and consistently demonstrated improved early-stage bone healing around the implants, resulting in a greater bone-implant contact area and better mechanical stability[8,16,17,29].

Laboratory (*in vitro*): Research on Melatonin exposure demonstrated an increase in osteoblastic survival when cultured in the laboratory, along with increased early-stage levels of bone matrix proteins[19,20]. Other analyses suggested that melatonin effects are even more pronounced when cells are grown on titanium implant material, suggesting a favorable interaction that melatonin may have with/for implants[18,23,30].

Early clinical data: Human data is still low in volume. However, a small number of clinically-relevant studies that provided a limited application of melatonin during the implant procedure have been published. One study found that when administered with local melatonin application, patients receiving implants had more implant stability and increased bone density radiographically during a follow up appointment[31]. The healing time also appeared to be shorter. Although these findings are exciting, the findings of these studies should be confirmed through larger studies to elucidate best practices[32].

POTENTIAL USES FOR MELATONIN IN IMPLANT DENTISTRY

Melatonin has several ways it may be used around implants:

Local application at the surgical site: This delivery method applies melatonin directly where it is needed. Melatonin may be applied to allograft materials, either in gel form as a topical layer within the graft or as a topical agent placed in the socket during the healing period[8,31]. The purpose is to concentrate melatonin actions at the site of integration.

Systemic supplementation: Oral melatonin has promise, especially where patients have marked oxidative stress or prolonged healing. However, the systemic approach is non-targeted and it is unclear how much melatonin reaches the implant site[5].

Implant surface coatings: Novel research is looking to incorporate melatonin onto implants' surface, creating coatings that may provide a gradual delivery of melatonin over time, while fostering healing in the immediate weeks after surgery[10,30].

Table 2: Current limitations of melatonin in implant dentistry: Dosage uncertainties, delivery methods, local bioavailability, release kinetics and lack of long-term human data

Current limitations	Description/Rationale	References
Optimal dosage and method of delivery remain uncertain	No consensus exists on the most effective dose or delivery route delivery route of melatonin	Cutando *et al.*[4], Reiter *et al.*[5], Sanidhya *et al.*[6] and Ahmadpour *et al.*[8]
Local bioavailability and release kinetics not well defined	The behaviour of melatonin at implant sites, its absorption, release and retention, is poorly characterized	Ahmadpour *et al.*[8], Ismail *et al.*[27] and Kiran *et al.*[28]
Limited long-term human data	Few studies assess extended follow-up in humans, especially in diverse risk groups	Hazzaa *et al.*[31], López-Valverde *et al.*[32] and Ravella *et al.*[33]

Table 3: Future directions for melatonin in implant dentistry: Combination with osteoinductive agents, development of controlled-release implant coatings and large clinical trials in high-risk patients

Future directions	Rationale/Key points	References
Evaluate the combined use with other Osseo inductive agents	Combining melatonin with growth factors, bone grafts or biomaterials may enhance osteogenesis and implant stability	Tresguerres *et al.*[10], Gómez-Moreno *et al.*[11] and Wang and Yeung[14]
Develop responsive coatings for controlled melatonin release	Surface coatings on implants could provide sustained local delivery, improving bioavailability and reducing dosage uncertainty	Tresguerres *et al.*[10], and Gómez-Moreno *et al.*[11]
Conduct large clinical trials in high-risk groups (diabetics, smokers, the elderly)	High-quality evidence is needed to establish efficacy, safety and optimal dosage in populations with compromised bone healing	Hardeland[12], Srinivasan *et al.*[13] and Wang and Yeung[14]

POTENTIAL BENEFITS OF MELATONIN

There several possible reasons melatonin continues to be seriously considered in implant dentistry:

- It is naturally occurring and already synthesized in the body, leaving less risk for adverse reactions[4,11]
- It has multiple favorable effects, promotes bone formation, reduces inflammation and is protective against oxidative stress[5,6,12,19]
- It is easily obtainable and low-cost relative to other biologic supplements used for bone regeneration[3]

These factors support that melatonin provides a simple and accessible opportunity to promote implant outcomes in at-risk populations[8,32].

QUESTIONS STILL TO BE ANSWERED

While the data and anecdotal evidence have shown promise for melatonin, there remain questions to be answered by further research:

- What is the ideal dose of melatonin for osseointegration?
- What amount of time and in what application method?
- Will there be long-term effects and potential interactions with existing medications?
- Do effects vary across patient sub-populations (elderly, diabetics, smokers)?

Until additional clinical trials have been conducted, it may be unwise to recommend melatonin as standard practice in implant dentistry and more appropriately used as off-label or experimental (Table 2).

WHAT IS NEXT?

Future studies may be directed at additional combinations of melatonin and other similar agents to investigate if the effects may be multiplied (Table 3). There is also interest in personalized augmentations based on each individual's distinct healing potential and inflammatory state. By that time, novel applications of implanted materials may one day allow for smart surfaces to deliver melatonin and other agents in a controlled manner that responds directly to the needs of the healing environment[8,30].

DISCUSSION

The evidence presented suggests that melatonin may have a favourable effect on the biological events associated with osseointegration[3,4,6,8,19,20,29-33]. *In vitro* and *in vivo* studies have indicated that melatonin assists in the differentiation and activity of osteoblasts, reduces osteoclast resorption and contributes to early vascularization at implant sites[6,15,19,20,22,24,29]. Such combined cellular and molecular effects may potentially result in improved bone-to-implant contact and mechanical stability in the early stages of healing. The mechanisms elucidated correspond well to the wider literature pertaining to bone physiology, where melatonin appears to act as both an antioxidant and immunomodulator. Its ability to modulate redox status and the inflammatory cytokines associated with the surgical intervention and subsequent healing may be of particular relevance. In spite of these encouraging data, there is still a reduced translational effect evident between experimental evidence and clinical use. The bulk of the evidence is from small animal studies with short follow-up periods. Larger randomized clinical trials will be required to substantiate whether the benefits found in the preclinical laboratories can be reproduced and if they will prove clinically significant in the human population.

Melatonin may be produced in the laboratory by microorganisms or plants[34,35]. Numerous methodological issues remain unresolved. The pharmacokinetics of melatonin delivered locally have not been very well described and systemic supplementation muddies the question of local bioavailability. In addition, interactions with other commonly used agents in implant dentistry, such as platelet-rich fibrin or bone graft materials, have not been adequately investigated. It is the lack of these answers, together with the striving for clear clinical guidelines, that makes these issues still confusing. The idea of coating implants with melatonin is an attractive one, which could possibly produce local sustained release directly into the peri-implant environment. Initial work on the modification of titanium surfaces has produced results that give hope that improved osteoblast adherence, with consequent diminished oxidative injury to tissues in the area, may occur[6,8,17,18,29,32]. It must be said that the long-term stability of such coatings, the release kinetics and the possibility of their degradation are little understood under physiological conditions. However, the safety aspect of melatonin should be stressed, where salubrious consequences of its longer duration exist. Melatonin is produced in organisms endogenously. Its use pharmacologically at surgical sites is, however, relatively recent. The possible systemic effects of repeated usage or dosage have not been individually or in combination thoroughly studied, particularly in the elderly or those with comorbid conditions such as diabetes. Evaluation of risk and benefit is of utmost importance.

The clinical potential of melatonin appears to be most relevant in conditions where oxidative stress or deficient bone metabolism results in impairment of normal healing processes, e.g., in smokers and patients with metabolic disorders. In such groups, the antioxidant and anti-inflammatory properties of melatonin may well compensate for the retardation or decreased regenerative capacity that is often observed. Nevertheless, in any use that may be either empirical or directly experimental, evidence will be required in the form of evidence-based dosing and legislative validation. Future studies should be carried out using a multidisciplinary approach. Comparative studies combining melatonin with other Osseo inductive materials could reveal synergistic effects. Long term in vivo studies, however, will be required in order that implant survival, peri-implant bone stability and histological integration can be studied. Concurrent work in materials science may lead to the establishment of appropriate delivery systems for melatonin, allowing control of its release subject to the various physiological needs encountered during the various stages of healing.

CONCLUSION

Melatonin shows promising potential in enhancing osseointegration. Its ability to stimulate bone-forming cells, modulate inflammatory responses and reduce oxidative stress makes it a valuable adjunct in implant therapy. Although current evidence is insufficient to support its generalized clinical use, literature suggests that melatonin could be particularly beneficial in patients with factors that may impair healing. Future research is expected to further clarify its role in optimizing implant outcomes over time.

SIGNIFICANCE STATEMENT

This study revealed the modulatory effects of melatonin on bone formation, inflammation and oxidative stress that can be beneficial for improving implant osseointegration and patient healing outcomes. By highlighting its potential as an adjunct in implant dentistry, this study will help researchers uncover the critical areas of melatonin's role in bone-implant interactions. Thus, a new theory on melatonin-mediated enhancement of osseointegration may be arrived at.

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