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The Effect of Melatonin and Its Agonist on Bone Metabolism: A Scoping Review

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ABSTRACT

Objectives : To assess the effects of melatonin and its agonist on bone tissue through a scoping review of the literature.

Materials and Methods: The keywords were searched on Scopus, Web of Science, and PubMed. Title and abstracts were reviewed to exclude the duplicates and irrelevant articles. The full-text articles were then screened in accordance with the inclusion criteria.

Results: Of the 5,383 identified articles [PubMed=5,508, Web of Science=122, Scopus=53], only 3 studies qualified to be included in the scoping review based on the inclusion criteria. The first study assessed effects of the oral melatonin on bone integrity and mass in postmenopausal osteopenic women through dual X-ray absorptiometry, quantitative computed tomography (QCT), high-resolution peripheral QCT (HR-pQCT), determined calciotropic hormones and bone markers. The other two studies evaluated radiographic and clinical outcomes such as Perio test, Angulated Bleeding test, Pink Esthetic Score (PES), Gingival index (GI), Peri-implant sulcus depth (PD), Wound healing index (WHI), Linear measurements of bone loss around implant and Densitometric analysis of dental implants with the local application of melatonin. All studies showed an improved outcome parameters in comparison with the control group.

Conclusion: Based on the findings of the included studies, it was found that melatonin improved bone mineral density, increased marginal bone level and minimized root resorption aiding in implant stability. The findings were suggestive that melatonin has osteoinductive properties and inhibitory effect on osteoclastic activity.

Keywords: Melatonin, Bone remodelling, Pineal hormone, Osteoblast, Osteoclast, Orthodontics.

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INTRODUCTION

Melatonin [N-acetyl-5-methoxy-tryptamine], a serotonin derived endogenous hormone primarily secreted by the pineal gland influenced by the suprachiasmatic nucleus has been involved in many physiological functions like blood pressure regulation, hormonal balance, circadian rhythm, immunomodulation, modulation of inflammation, ovarian physiology, angiogenesis and antioxidant property.[1–3] Melatonin secretion follows a circadian rhythm, peaking at night and troughing during the day, regardless of the species.[2, 4-5] While the primary source of melatonin is the pineal gland, secondary sources include the retina, adrenal gland, heart, liver, kidney, lung, arteries, and T, B lymphocytes.[1-2,6] Furthermore, few studies have found detectable levels of melatonin in plasma, saliva, and gingival crevicular fluid. [7–10]

Exogenous melatonin has a diverse range of effects on physiologic processes, including the management of insomnia, behavioral disorder in children with severe psychomotor retardation, substantial sleep disorders,[2,11] such as Smith-Magenis syndrome, [2,12] Rett syndrome, [13]Asperger disorder, [2,14] and intrinsic circadian disorders like jet lag, delayed sleep phase syndrome and night work shift schedules.[2,4,6] Studies have shown lowered levels of melatonin in plasma, saliva and GCF level, that occurs as a consequence of microbial infection, a dysregulated immune response and generation of free radicals and reactive oxygen species in periodontal diseases.[7]

The benefits of melatonin with regards to dentistry is in its bone healing property. The application of melatonin in hard tissues, such as bone and teeth, has recently drawn a lot of interest. On literature search, the effect of melatonin in relation to bone remodelling, bone repair, osteoporosis, dentin formation, osteointegration of dental implants have been extensively studied, though there is a lack of summative review.[3,15–19] As a result, the current scoping review was conducted with the aim of assessing the existing research on the effect of melatonin and its agonist on bone tissue. The outcome of this review will be beneficial in supporting the therapeutic use of exogenous melatonin in orthodontics for periodontally compromised patients and to decelerate tooth movement.

MATERIALS AND METHODS

Research Question: Does the use of exogenous melatonin has an effect on bone tissues

Search strategy:

A scoping review search was carried out to retrieve papers from Web of Science, Scopus, and PubMed from 1980 until October 2022. The search strategy was done by using following keywords: [Melatonin OR Pineal Hormone OR Ramelteon OR Agomelatine OR Tasimelteon] AND [Bone OR Osteoblast OR Osteoclast OR Bone remodeling OR Bone Metabolism] AND [Orthodontics]. The current study was registered in PROSPERO Database (CRD42022372208). The workflow of the review is provided in Figure 1.

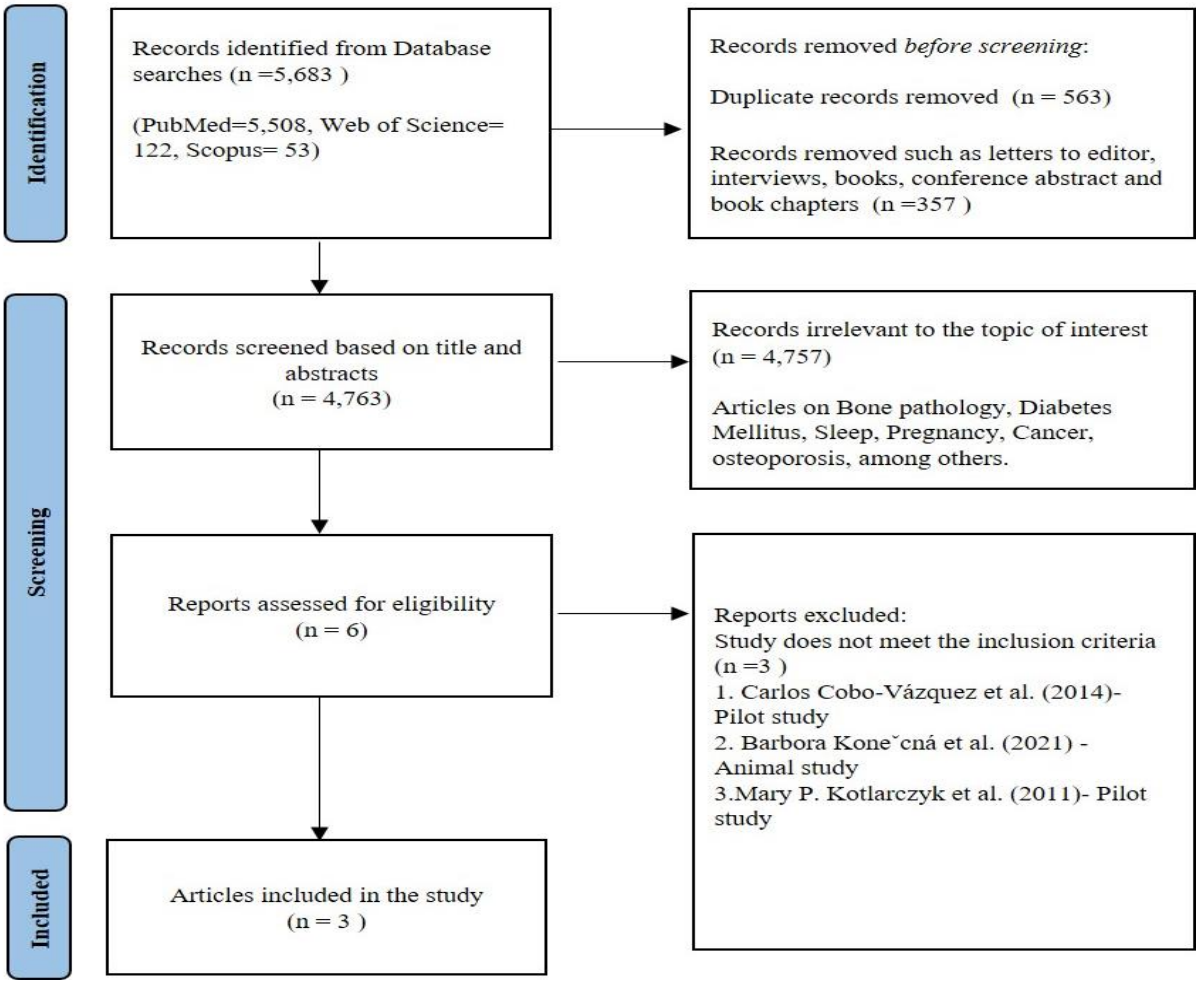

Figure 1 – *The workflow of the present scoping review was followed as per PRISMA guidelines.*

Inclusion criteria:

The following inclusion criteria were included for this review: Human clinical trials and randomized control studies on the effect of melatonin and its agonist on Bone tissue. Studies on implant stability and periodontium were also included.

Exclusion criteria:

Exclusion criteria included animal studies, studies that did not evaluate bone health, case reports, opinions, editorials, interviews, and letters, as well as studies written in languages other than English.

The search hit recognized with a total of 5,683 articles, from which 563 duplicates and 357 records such as letters to editors, books, interviews, conference abstract and book chapters were removed. This was followed by screening of the articles based on the title and abstract, of which 6 were included based on relevancy and inclusion criteria of the current study. Following a thorough reading of the full articles, three studies were included.

Focus Question: Does exogenous melatonin have an effect on the metabolism and remodeling of bone tissues?

PICO:

Participants/population: Voluntary adult participants [Male=15; Female=106].

Intervention[s], exposure[s]: Oral or topical form of Melatonin administered for the experimental group.

Comparator[s]/control: Control groups were administered with placebo or saline.

Outcome: The outcomes were measured in terms of wound healing, new bone formation, and bone mineral density as well as implant stability.

RESULTS

Characteristics of included studies [Table 1]:

Study design: The studies meeting the inclusion criteria were three Randomized control trials.

Participants: The three RCTs involved a total of 121 adult participants [Male=15; Female=106].

Intervention: Melatonin dosage varied from 1-3mg/day on oral administration in the study by Anne et al [20] whereas in other two studies on implants, topical gel and powered form of melatonin had been used at the site of implant insertion.[18,19] The data set from each article was analyzed based on the study design, patient sample size, dosage, and route of drug administration, as well as the physiological changes in bone.

Outcome: The outcomes of these three publications differed in terms of wound healing, new bone formation, and bone mineral density and were measured using high-resolution peripheral QCT, quantitative computed tomography, calciotropic hormones and bone markers and dual X-ray absorptiometry,[20] Digital Panoramic radiograph, CBCT, Perio test, Angulated Bleeding test, Pink Esthetic Score (PES), Gingival index (GI), Peri-implant sulcus depth (PD), Wound healing index (WHI), Linear measurements of bone loss around implant and Densitometric analysis of dental implants but the melatonin groups' statistics were all higher [study groups].[18,19]

Results of individual studies:

In the first study,[20] 81 postmenopausal osteopenic women were randomly assigned to one year of nightly melatonin 1 mg [N = 20], 3 mg [N = 20], or placebo [N = 41] treatment in a double-blind RCT. They had evaluated the bone mineral density [BMD] using high-resolution peripheral QCT, quantitative computed tomography, and dual X-ray absorptiometry at baseline and after a year of treatment, as well as bone markers and calciotropic hormones. The average age of the study participants were 63 years. Melatonin increased femoral neck BMD by 1.4 percent [P 0.05] in a dose-dependent manner [P 0.01], with BMD increasing by 0.5 percent [P = 0.55] in the 1 mg/day group and by a 2.3 percent [P 0.01] in the 3 mg/day group. In the 3 mg/day melatonin group, tibial trabecular thickness increased by 2.2 percent [P = 0.04], whereas the spine volumetric bone mineral density increased by 3.6 percent [P = 0.04]. Treatment had no influence on bone mineral density at other sites or levels of bone turnover biomarkers; however, 24-hour urine calcium was reduced by 12.2% [P = 0.02] on influence of melatonin.

In the second study,[18] 1 ml of 1.2 mg/ml melatonin gel was administered into each osteotomy site prior to implant insertion. This study was followed by radiographic analysis, Perio test, pink esthetic score & probing depth was done to examine the stability of implant and bone resorption at the site. 14 patients with missing maxillary premolars were randomly assigned to receive 14 one-piece implants that were promptly loaded two weeks after

initial implantation. Group I included seven implants with acid etched surfaces, while Group II included seven implants with acid etched surfaces as well as local application of melatonin gel at the osteotomy site. At 1, 3, 6 and 12 months after loading, the patients were contacted for follow-up. After a year of monitoring, all of implants were deemed successful. After one month of implant loading, there was considerably higher implant stability in the study group. Distal probing depth and marginal bone loss decreased significantly in the study group.

In the third study, [19] they divided 26 patients with two non-restorable anterior/premolar teeth into two equal groups at random. Dental implants were immediately inserted, either with ABG [control group] or ABG/melatonin [study group]. As outcome measurements, gingival index [GI], peri-implant sulcus depth [PD], and wound healing scores were used. At baseline, 6, and 9 months, cone beam computed tomography was obtained. At the end of the experiment, the mean of marginal bone loss was significantly different [p = 0.0001] between the control group [1.91 mm ± 0.42] and the study group [0.84 mm ± 0.34]. The study group's bone density increased considerably, from 420.14± 38.33 in the control group to 500.73± 40.92 in the study group [p = 0.0001]. In GI, the difference seen between control group [0.68 ±0.42] and the study group [0.45 ±0.49; p = 0.044] was statistically significant. The study group's PD was markedly reduced at the end of the trial [0.42 mm± 0.50; p = 0.002], and the healing scores were also significantly improved [p = 0.026].

Table 1: Characteristics of Included Studies

Authors	Study design and Population	Sample size	Intervention	Methodology	Outcome assessment	Inference
Anne Kristine Amstrup et al, 2015, Denmark.	RCT, Adults	81, F=81	1, 3mg, oral	Post-menopausal women were administered with oral melatonin for 1 year, nightly.	Bone mineral density [BMD] by dual X-ray absorptiometry, quantitative computed tomography [QCT], high-resolution peripheral QCT [HR-pQCT], determined calciotropic hormones and bone markers.	Dose dependent increase in BMD by 2.3% at femoral neck in response to 3mg melatonin group compared to placebo. Additionally , increase in BMD in lumbar spine in higher dosage group. And increase in trabecular thickness in the distal tibia & reduction of urinary calcium in combined melatonin group.
Mona Yehia Abdelhalem Elgammal et al, 2016, Egypt.	RCT, Adults	14, M=5, F=9	1 ml of 1.2 mg/ ml of Melatonin gel	1 ml of 1.2 mg/ml of the prepared melatonin gel was injected in each osteotomy site before loading the implant, one year follow-up.	Radiographic analysis, Perio test, Angulated Bleeding test, Peri implant probing depth & Pink esthetic score was done to examine the stability of implant and bone resorption at the site.	Significant decrease in the Marginal bone loss & depth of the distal pocket in the study group.
Hala, Hazzaa et al, 2019, Egypt.	RCT, Adults	26, M=10, F=16	Melatonin powder; mixed with saline and ABG	ABG fragments collected during implant site preparation were mixed with melatonin powder and saline for the experimental group.	Gingival index (GI), Peri-implant sulcus depth (PD), Wound healing index(WHI), Radiographic evaluation (Digital Panoramic radiograph & CBCT),Linear measurements of bone loss around implant, Densitometric analysis.	Compared to control group, the test group reflected a significant benefit at 6 & 9 months, with decrease in Marginal bone loss, Pocket depth & gingival index. As well as increase in wound healing and bone density.

DISCUSSION

The first study included in this review found that melatonin treatment improved bone mineral density in postmenopausal women at multiple sites. [20] According to Sandyk et al, a decrease in melatonin production occurs after menopause, resulting in lower plasma calcium levels. Since PTH is immediately secreted in response to a decrease in plasma calcium levels, decreased melatonin secretion may accelerate osteoporosis.[21] Harms et al found that postmenopausal osteoporotic women had altered pulse amplitude and frequency modulation of PTH secretion in an investigation. [22] Furthermore, unlike normal men, postmenopausal osteoporotic women did not show a diurnal regularity of PTH secretion, as found by Markowitz et al. During the postmenopausal period, this mechanism hastens the onset of osteoporosis. [23] Since, melatonin has been reported to increase the osteoblast metabolism, Uslu et al used animal experimental model to investigate the histomorphometric, densitometric, or biochemical impacts on postmenopausal osteoporosis when melatonin was administered to ovariectomized rats. The increase in the quantity of cortical and trabecular bone after exogenous injection of melatonin was quantified using histomorphometric methods in his study. They concluded that melatonin may be an effective treatment for postmenopausal osteoporosis, although it was found to be contraindicated in women with normal ovarian function.[17]

The other two studies in this review on immediate loading of implants [Mona-El-Gammal et al., Hala.H.A.Hazzaa et al] revealed that melatonin reduced gingival index, probing depth, and marginal bone loss while enhancing implant stability, bone density, and wound healing.[18,19] A systematic review on the topical applications of Melatonin in dental implants stated an increase in bone implant contact [BIC] and new bone formation around dental implants.[24] They suggest that the increase in BIC is caused by melatonin's direct action on osteoblasts, which leads to an enhanced rate of preosteoblast maturation into osteoblasts, both in terms of number and velocity, as well as an increased rate of osseous matrix synthesis and calcification.[24] Furthermore, other research indicates that melatonin may promote bone formation through other mechanisms, such as the stimulation of genes that regulate the presence of specific proteins in the osteoid matrix.[3,25] Melatonin also suppresses free radical production in osteoclasts and regulates osteoclastic activity by detoxifying free radicals produced during osteoclastogenesis via its antioxidant abilities. Bone resorption is inhibited as a result of the above.[15-16,26] According to the findings of a study conducted by Jang-Ho Son et al, melatonin can promote preosteoblastic MC3T3-E1 cell differentiation and mineralization in hypoxic culture conditions, as well as osteoblastic differentiation of these cells via the Prkd1 and p38 MAPK signaling pathways.[27] The results of the study as well as existing literature demonstrates an osteogenic potential of Melatonin on bone tissues. We were able to get only three RCTs in relation to the topic of interest, more RCTs are needed in this field to get a broader perspective of the effects of melatonin on bone metabolism.

CONCLUSION

Based on the findings of the included studies, it was found that melatonin played a proactive role in decreasing bone loss and also in increasing the bone mineral density. This scoping review is suggestive of an osteoinductive potential of melatonin on the osteogenic tissues. But to confirm affirmatively the role of melatonin on osteogenic tissues, more RCTs with adequate sample size will be needed in future.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

All the authors approved the current version of the article for publication.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest exist.

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There are no funding agencies involved in the present study.

AUTHORS' CONTRIBUTIONS

ST, UG, KM and RB were involved in the design of the study. ST, UG, KM and RB were involved in the data collection, methodology, screening, and interpretation of the results. ST drafted the manuscript. UG critically reviewed the manuscript and supervised the entire study. All the authors approved the current version of the article.

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