THE POTENTIAL CAPABILITY OF MELATONIN TO ANTICIPATE POSTORTHODONTIC TREATMENT RELAPSE: A LITERATURE REVIEW

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THE POTENTIAL CAPABILITY OF MELATONIN TO ANTICIPATE POST-ORTHODONTIC TREATMENT RELAPSE: A LITERATURE REVIEW

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ABSTRACT : The long-term stability outcome is the main goal of orthodontic treatment. Retainers are the most commonly used appliances to prevent orthodontic relapse. However, they are not always sufficient to manage post-orthodontic treatment relapse. An effective approach is required to anticipate the occurrence of orthodontic relapse. This review was aimed to discuss the potential use of melatonin to modulate post-orthodontic treatment relapse. Melatonin may become a promising agent to regulate orthodontic relapse, through modulating alveolar bone remodeling by stimulating osteoblast and inhibiting osteoclast. Administration of melatonin in rodents model promotes bone mass, bone formation, impairs bone healing and inhibits bone loss. In addition, nightly melatonin supplementation in perimenopausal women is well tolerated and may improve the imbalance in bone remodeling. Melatonin also accelerates osteogenic differentiation in various cell cultures through melatonin 2 receptor (MT2R) by activating multiple signal cascade including MEK1/2 and 5, Wnt 5 α/β, BMP-2 and -4, PDGF/AKT signaling pathway. Furthermore, melatonin has also been reported to suppress osteoclastogenesis directly through melatonin 1 receptor (MT1R)/MT2R by inhibiting NF-κB signaling pathway and indirectly by decreasing RANKL/OPG ratio from osteoblast. Thus, melatonin may provide a new direction in controlling post-orthodontic relapse, by stimulating bone formation and inhibiting bone resorption.

Key words : Melatonin, orthodontic relapse, osteoblast, osteoclast, medicine.

INTRODUCTION

The primary goal of orthodontic treatment is to achieve a long-term stability outcome (Nugraha *et al*, 2019). In orthodontic tooth movement, the usage of both fixed and removable retainer is essential to inhibit the tooth return to their original positions after treatment, enabling periodontal tissues remodeling and maintain the space balance. On the other hand, this condition is difficult to obtain, and insufficient periodontal tissue remodeling often leads to orthodontic relapse (Han *et al*, 2010; Vieira *et al*, 2015; Liu *et al*, 2017). Generally, the prevalence of relapseis relatively high, ranges between 10% to 50%, depending on their follow-up time. In prolonged follow-up time, its prevalence became 30% of cases (Sadowsky and Sakols, 1982). Meanwhile, other studies stated that relapse occurred between 30%-50% cases after 10 years and declined to 10% cases after 20 years (De Bernabé *et al*, 2017; Yu *et al*, 2013).

Relapse can be caused by multifactorial factors, such as muscle disoders,changes in dental arch form, supracrestal fibers reorganization and reorientation insufficiency, lasting unwanted habits, improper skeletal growth, immature and slightly mineralized bone tissue surrounding the moved tooth (Vieira *et al*, 2015). The most general approach to obtain the long-term stability outcome is the use of a retainer. In the first 6 months, retainer must be used full-time and nightwear is necessary for at least 12 months. Long duration of active orthodontic treatment and the addition of a 2-year retention time frequently cause disappointment in patient. Thus, leading to rejection or poor patient compliance to wear retainer and cause the occurrence of relapse. Therefore, an effective method is required to modulate treatment stability and to shorten retention time (Zhang *et al*, 2014).

Enhancement of osteoblast activity and suppression of osteoclast activity in alveolar bone during the retention phase might effectively inhibit relapse and improve stability post orthodontic tooth movement, as the relapse pressure remains until alveolar bone remodeling is complete (Sitasari *et al*, 2020; Inayati *et al*, 2020; Hermawan *et al*,

2020; Nugraha *et al*, 2020). Recently, many researches stated that administration of pharmacological agents might turn into a convincing approach to prevent orthodontics relapse, which are local or systemic supplementation of bisphosphonate (Utari *et al*, 2020), simvastatin (AlSwafeeri *et al*, 2018; Vieira *et al*, 2015), aspirin (Liu *et al*, 2017), CMT-3 (Vieira *et al*, 2019) and raloxifene (Azami *et al*, 2020).

Melatonin is an endogenous hormone synthesized mainly by the pineal gland and has recognized to be related with bone. Melatonin stimulated bone formation and suppresses bone resorption. In various studies, melatonin was demonstrated to promote human mesenchymal stem cells (hMSCs) and preosteoblast differentiation into mature osteoblast through various signal transduction pathway including ERK 1/2 and Wnt/beta-catenin (Maria *et al*, 2018; Younho *et al*, 2017; Park *et al*, 2011). In addition, Koyama *et al* (2002) and Pramusita *et al* (2018) stated that melatonin administration suppressed osteoclastogenesis trough down-regulation of RANKL. Supplementation of melatonin was also found to enhance bone healing by inhibiting osteoclastogenesis through reducing RANKL expression (Histing *et al*, 2012). The purpose of this article was to discuss the potential role of melatonin to anticipate post-orthodontic treatment relapse through modulating alveolar bone remodeling.

Melatonin

N-acetyl-5-methoxytryptamine, which is known as melatonin, is an indolamine hormone that is synthetized mainly by glands and some extra pineal tissues. Melatonin synthesis occurs when enzyme tryptophan hydroxylase hydroxylates tryptophan to 5-hydroxytryptophan, which is then decarboxylated into serotonin. Followed by the conversion of serotonin to melatonin after undergoing acetylation by the enzyme arylalkyl amine N-acetyltransferase and methylation by the enzyme hydroxy indole-O-methyltransferase (Emet *et al*, 2016; Maria and Witt-Enderby, 2014).

The onset of dark is identified by the retina and these photic stimuli subsequently transmitted to the hypothalamus gland through the suprachiasmatic nucleus (SCN) and the sympathetic nervous system. Therefore, stimulates the secretion of norepinephrine to promote melatonin production by increasing α1 and β1 adrenergic receptors expression and arylalkyl amine N-acetyltransferase activity. On the other hand, retinal photoreceptors experience hyperpolarization during the day, thus inhibiting the release of norepinephrine (Ostrin, 2019; Maria and Witt-Enderby, 2014).

Humans have the melatonin hormone, which reaches the bloodstream through passive diffusion and melatonin production elevates immediately after an absence of light, reaches peak concentrations in the night between 2-4 a.m. and gradually declines. The concentration of melatonin in serum varies according to age. Infants younger than three months old only secrete few melatonin. Melatonin secretion will increase at the age of 1-3 years and reach the highest concentration at night (an average of 325pg/mL or 1400 pmol/L), after which it will decrease continuously. In normal young adults, the general daytime melatonin concentration is 10 pg/mL or 260 pmol/L and reaches its peak at night at 60 pg/mL or 260 pmol/L. Along with aging, the peak level of melatonin will be reached more than 1 hour later than normal time and the peak level of melatonin is only 50% of the level of young adults (Waller *et al*, 2016; Maria and Witt-Enderby, 2014).

Melatonin production is strongly influenced by the level of light received, so lighting during sleep affects the quality. Melatonin is important because it plays a role in regulating sleep and wake cycle in individuals. Melatonin also affects the endocrine, immune and cardiovascular systems. A person, who has insufficient sleep habits will experience circadian rhythm disorders, changes in the level of the hormone melatonin in the body, and the habit that lasts longer will affect other body systems (Ostrin, 2019; Auld *et al*, 2017).

Melatonin is rapidly metabolized to 6-hydroxymelatonin through hydroxylation by cytochrome P450 and subsequently conjugated with sulfuric or glucuronic acids and at the end will be secreted through urine. The major metabolite of melatonin, 6-sulfatoxymelatonin has parallel levels with serum melatonin levels. Intravenous administration of melatonin will be rapidly distributed and eliminated. While the bioavailability of melatonin administered orally differs greatly (Maria and Witt-Enderby, 2014).

Melatonin has 3 kinds of receptors, namely melatonin 1 receptor (MT1R), melatonin 2 receptor (MT2R) and melatonin 3 receptor (MT3R). MT1R and MT2R have the same binding character, the binding agonist is guanosine triphosphate (GTP)-sensitive. MT3 is a quinone reductase 2 enzyme that accomodates cell protection against oxidative stress. Melatonin receptors of MT1R and MT2R are G protein coupled receptors found in numerous places in the SCN. Melatonin receptors mediate intracellular events, which are cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP) and calcium levels changes; stimulation of certain protein kinase C and intracellular steroid hormone receptors and modulation of proteins

Table 1 : Melatonin effect on bone.

Samples	Dosage	Route of administration	Conclusion	Author
hMSCs co-cultured with human peripheral blood monocytes	50 nmol/L	Incubated with melatonin	Melatonin promotes osteoblast differentiation through MT2R, MEK1/2, and MEK5	Maria *et al* (2018)
MMTV- neu transgenic mice MMTV-*neu* transgenic mice	15 mg/L	Oral administration	Melatonin supplementation increases pErk1/2, pErk5, Runx2, OPG and RANKL levels in bone	
Mouse pre-myoblast cell line, C2C12	0.1-2 uM	Incubated with melatonin	Melatonin directly modulates the late stage of osteoblastic differentiation by increasing Osterix stability and expression through PKA and PKC signaling pathways	Han *et al* (2017)
Osteoblast precursor MC3T3 E1 cells	50 nM	Incubated with melatonin	Melatonin accelerates osteoblastic differentiation through PDGF/AKT signaling pathways by increasing ALP, collagen type I α1 chain, osteocalcin and Runx2 levels	Zhu *et al* (2020)
C57BL/6J mice	50 mg/kg/day	Intraperitoneal injection	Melatonin administration enhances osteoblastic diûerentiation, callus formation and inhibits osteoclastic differentiation in mice with femoral fracture	
Sprague-Dawley (SD) rats	50 mg/kg/day	Intraperitoneal injection	Melatonin treatment enhances bone mass in elderly rats with osteoporosis and improves the femoral trabecular microstructure, plays a role in bone formation by suppressing osteoclast activity, stimulating osteoblast activity, and decreasing the formation of adipocytes.	Chu *et al* (2017)
hBMMSCs	0.01-150 uM	Incubated with melatonin	Melatonin directly stimulates osteoblast differentiation.	Calvo-Guirado *et al* (2015)
Mouse BMMs	0.01 nM–100 uM	Incubated with melatonin	Melatonin 1-100 uM directly suppress osteoclastogenesis of BMMs through ROS-dependent inhibition of NF-κB signaling pathway, but not a SIRT1-independent pathway.	Zhou *et al*(2017)
Mouse BMMs	500 uM	Incubated with melatonin	Melatonin-mediates anti-osteoclastogenesis as a result of down-regulating NF-κB pathway and subsequent inhibition of NFATc1 transcription factor activation, through MT1R/MT2R melatonin membrane receptors.	Kim *et al* (2017)
C57BL/6J mice	5 and 50 mg/kg/day	Intraperitoneal injection	Melatonin supplementation improves retinoic acid-induced osteoporosis condition by increasing bone mass and bone density as well as decreasing the number of osteoclasts.	Wang *et al* (2019)
RAW264.7 murine monocyte /macrophage cell lineand MC3T3-E1 cells	100 nM	Incubated with melatonin	Melatonin restores the effect of retinoic acid, by decreasing the number of osteoclasts, osteoclast differentiation marker, oxidation indexes, p-p65 and p-IκBα expression in RAW264.7 cells as well as increasing osteogenic differentiation markers, antioxidant enzymes, p-ERK and p-SMAD1 expression in MC3T3-E1 cells.	
C57BL/6J mice	10 and 100 mg/kg/day	Oral administration	The application of melatonin can reverse bone loss and microstructure disorder in osteoporotic mice	Zhou *et al* (2020)
Mouse BMMSCs and BMMs	10 and 100 nM	Incubated with melatonin	Physiologic dose of melatonin promotes osteogenic differentiation of BMMSCs through inhibiting MT2R-dependent canonical NF-κB signaling	

Table 1 continued...

			pathway and down-regulates BMMSC-mediated osteoclast formation by decreasing RANKL expression in indirect co-cultured system.	Nakano *et al* (2019)
Inseminated eggs (*Gallus gallus domesticus*)	5, 50, 500 ug	*In ovo* injection	Melatonin injection decreases cathepsin K and matrix metalloproteinase 9 (MMP9) expression level, while increases calcitonin expression level.	
Newly hatched chick calvariae bone cells	10^{-7}M or 10^{-3}M	Incubated with melatonin	Melatonin stimulates calcitonin expression and concentration in a dose-dependent manner, however inhibits cathepsin K and MMP9 expression.	

from G protein signaling. Melatonin receptors are also found in mesenchymal stem cells (Emet *et al*, 2016; Jiabei Liu *et al*, 2016).

The potential capability of melatonin in preventing orthodontic relapse

Orthodontic tooth movement is a tightly coordinated and balanced process, which involves alveolar bone remodeling in response to orthodontic force (Narmada *et al*, 2019). The cellular response to mechanical force results in increased activity of bone-resorbing osteoclast under compression, as well as, bone-forming osteoblast in tension area (Nareswari *et al*, 2019; Hisham *et al*, 2019). Orthodontic relapse, is often occurred after orthodontic treatment, becoming a main clinical issue for both dentist and patients (Alhasyimi *et al*, 2018). Both removable and fixed retainers are the most generally used devices to retain the teeth in their new position following orthodontic treatment. Despite the long-term used of the retainers, yet in some cases, orthodontic relapse may be still present. The reported prevalence of relapse ranges between 2.67% - 42.2%, depends on many factors, such as the severity of the malocclusion, different monitoring times, retention time and active orthodontic treatment duration (Al-Jasser *et al*, 2020; Ligia Vaida *et al*, 2019; Vaida *et al*, 2019). Because relapse often occurs unpredictably and caused by multiple factors, an effective approach is needed to achieve long-term stability following orthodontic treatment and anticipate the occurrence of orthodontic relapse. Recent studies suggested that pharmacological agents-based therapy may become a promising method to regulate post-orthodontic treatment relapse, through modulating alveolar bone remodeling, decreasing osteoclast activity, and stimulating osteoblast formation (Azami *et al*, 2020; Dolci *et al*, 2017; Vieira *et al*, 2019).

Melatonin is a hormone released by the pineal gland according to circadian rhythm, which has small concentration during the day and high concentration at night. Melatonin can exert its physiological action by binding to its receptors, MT1 and MT2 and has favorable functions against sleep disorders (Auld *et al*, 2017), depression (De Crescenzo *et al*, 2017), memory impairment (Alzoubi *et al*, 2018), neurodegenerative disease (Kilic *et al*, 2017) and cancer (Liu *et al*, 2016).

Melatonin has the capability to maintain bone health, by regulating bone remodeling as the main target. Melatonin maintains the equilibrium between bone formation and bone resorption to renormalize bone marker turnover. Many studies have reported its effect on bone metabolism by stimulating osteoblast and inhibiting osteoclast. Melatonin accelerates osteogenesis as a result of various mechanism, which consist of stimulating the differentiation and mineralization of osteoblast (Table 1). Melatonin promotes osteogenic differentiation from hMSCs, C2C12, MC3T3-E1, C3H10T1/2 and bone marrow mesenchymal stem cells (BMMSCs) through MT2R by activating multiple signal cascade including MEK1/2 and 5 (Sethi *et al*, 2010; Maria *et al*, 2018), Wnt 5 α/β (Jiang *et al*, 2019), BMP-2 and -4 (Han *et al*, 2017), PDGF/AKT signaling pathway (Zhu *et al*, 2020) and its downstream signaling pathway, including RUNX-2 and OCN (Park *et al*, 2011; Calvo-Guirado *et al*, 2015). These *in vitro* studies consistent with *in vivo* studies describing that melatonin supplementation promotes bone mass and bone formation (Gürler *et al*, 2019; Chu *et al*, 2017), impairs bone healing (Yildirimturk *et al*, 2016) and alleviates bone loss (Wang *et al*, 2019) in rodents. Related to *in vitro* and *in vivo* studies, several human studies also established that melatonin has benefit on bone health. Kotlarczyk *et al* (2012) suggested that administration of melatonin for 6 months is well tolerated and may improve imbalance in bone remodeling to inhibit bone loss. Randomized control trial study also demonstrated that melatonin, strontium, vitamin D3 and vitamin K2 (MSDK) supplementation increases bone mineral density (BMD) in lumbar spine and left femoral neck, increases serum P1NP levels, reduces bone turnover (CTX:P1NP), and improves mood and sleep quality (Maria *et al*, 2017). Melatonin has also been found to have inhibitory effects on osteoclastogenesis from bone marrow monocytes

(BMMs) and RAW264.7 murine monocyte/macrophage cell line directly through MT1R/MT2R by inhibiting NF-κB signaling pathway (Zhou *et al*, 2017; Kim *et al*, 2017; Wang *et al*, 2019; Zhou *et al*, 2020) and indirectly by decreasing RANKL:OPG ratio from osteoblast (Pramusita *et al*, 2018; Koyama *et al*, 2002).

CONCLUSION

Melatonin may become a promising pharmacological agents-based therapy to control post-orthodontic relapse, by stimulating osteoblast formation and inhibiting osteoclast activity. However, further experimental studies are needed to propose this aim, both in post-orthodontic relapse *in vivo* models and clinical study in human.

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