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The Effects of Melatonin in Bone Healing

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Review Article

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Abstract

Melatonin, an endogenous hormone, regularly is produced in pineal gland. Suprachiasmatic nucleus and the light/dark cycle controls melatonin function. Melatonin doesn't act upon specific target tissue; it reaches all organs and tissues and enters all intra cellular structures like mitochondria and nucleus. Melatonin has an important effect on physiological processes of body including regulation of blood pressure, circadian rhythms, ovarian function, seasonal reproduction, and immune function. The general effects of melatonin in bone health were proposed by many researchers during the last years. First experiments studied the influence of the pineal gland on level of serum calcium. It has been saw that inhibition the melatonin biosynthesis by exposure of young rats to the fluorescent light decrease the concentration of calcium in the serum. The effects of melatonin on bone healing were investigated by scientists, and they observed which melatonin protects the bone from fracture. Studies have showed which melatonin has an influential role on bone-healing because of its regulation of bone cells, antioxidant properties, and promotion of angiogenesis actions. Scientists have been show that melatonin has aninfluential role in bone healing process due to its regulation of bone cells, antioxidant properties, and promotion of angiogenesis actions.

Keywords: Melatonin; Bone healing

Introduction

Aaron Lerner and colleagues 1958 found chemical structure of Melatonin as N-acetyl-5-methoxy-tryptamine [1]. Melatonin is an endogenous hormone which regularly is produced in pineal gland andsuprachiasmatic nucleus and the light/dark cycle controls its function [2]. Melatonin doesn't act upon specific target tissue; it

reaches all organs and tissues and enters all intra cellular structures like mitochondria and nucleus [3]. In addition melatonin synthesis occurs in other tissues, including skin, gastrointestinal tract, retina, lymphocytes and bone marrow [4]. Extra-pineal melatonin doesn't enter the blood flow and it may influence some physiological functions through paracrine signaling [5]. It has been shown that pinealectomy increases collagen degradation, increases in trabecular separation and decreases trabecular thickness, decreases the volume of cancellous bone, increases in bone resorption, inhibits of bone formation, decreases bone mineral density, decreases BMD, promote development of degeneration of intervertebral disc and bone loss and also bone remodeling [6]. But future studies are needed to establishedthe effects of melatonin on bone remodeling [7].

The Effects of Melatonin in Body

Melatonin has an important effect on physiological processes of body including regulation of blood pressure, circadian rhythms, ovarian function, seasonal reproduction, and immune function [7]. The in vitro and the in vivo studies have shown which melatonin has a potent scavenger action of the oxygen centered radicals [8]. Also the decrease in its serum level which occurs with aging, with several physiologic effects, has made some scientists to suggest which melatonin is effective in aging [9]. In addition there is evidence from that melatonin effects the growth of tumors in some animals [10]. When exogenous melatonin is administered it show hypnotic/sedative effect, temperature-lowering effects, protection hematopoietic tissue from the mortal effect of cancer chemotherapeutic agents, increase the proliferative response of rat lymphocytes, increases the number of nature killer cells, enhance on angiogenesis phases of wound healing, counteraction immune deficiencies, alteration the timing of fatigue and sleep and act as acute sleepiness-inducing, reduction of bone formation, and some effect on circadian rhythms and general health. Oral melatonin affects quality, duration and tendency of sleeping (speed of sleeping); and it probably has hypnotic effects [11]. Its action mechanism on different physiological processes is various [12]. But we can say that the actions of melatonin are mediated by indoleamine and its special receptors on membrane or nucleus [13]. In addition, Melatonin is lipophilic and passes through the cell membranes to gain access to different organelles [14]. It can also bind to cytosolic proteins such as calmodulin, kinase C and calreticulin [15].

Melatonin and Bone Metabolism

In Vitro Studies

One study demonstrated that after melatonin exposure osteoblasts showed an increase in expression of bone matrix sialo protein gene like other bone marker proteins, such as alkaline phosphatase, osteopontin and osteocalcin [16]. Also melatonin increases procollagen type I-peptide production [17]. Many studies substantiated which melatonin is a mediator in bone stimulation and formation [18]. At very low concentrations, melatonin stimulates the proliferation osteoblasts in cell culture [19]. In cultures of human osteoblasts, melatonin promotes the formation and production of mineralized matrix [20].

In Vivo Studies

First indication which melatonin administration has positive effectson decreasing bone loss has been obtained in ovariectomized animals. In rats with receiving melatonin by oral administration, a decrease in urinary deoxypyridinoline after ovariectomy, that is an index of the resorption of bone, was seen within four weeks post operation [21]. Another group of findings for effects of the melatonin in bone derived from researches about the animals with experimental scoliosis [22]. Scoliosis developed in pinealectomized animals, with anatomical characteristics like idiopathic scoliosis of human. Pinealectomy because anomalies of the vertebra and decrease of the mechanical strength of vertebrae .The possibility which melatonin and its receptors may cause congenital lordoscoliosis was also entertained [23]. Also the serum levels of melatonin in adolescents animals with idiopathic scoliosis were lower than in controls Acil, et al. 2004 [24]. Melatonin may prevent the destruction of skeletal system and bone; and encourage bone formation with its receptors [25]. One article has been published that investigated melatonin is a protective agent against bone cell damage induced by chlorhexidine [26]. It has been documented which melatonin protects osteoblasts in peri-implantitis and periodontitis treatment [27]. Another study has shown the effects of 5-methoxy-tryptophol on the function of osteoblast. But it has observed which melatonin must be in higher dose to promote better cell differentiation effects. Melatonin induces transcription of bone sialoprotein via CRE1 and CRE2 elements in bone sialoprotein gene promoter. Bone sialoprotein is a specific protein of mineralized connective tissue which expressed in the early phase of cementum and bone mineralisation [28]. Where, melatonin has advantageous effects on agerelated bone loss which improve of the biomechanical and microstructure estates

of aged bones [29]. In a recent study scientists used a melatonin graft in a procaine bone graft to the bone formation promotion in a rabbit model. They reported which melatonin has positive effect in quick regeneration of the length and width of bone. Melatonin acts as an osteo inductive comparing porcine bone [10]. The potential advantageous effects of melatonin on hard tissue and bone repair are angiogenesis and increase in bone density [30]. As a bone protective treatment against osteoporosis and bone lost, melatonin was studied on the perimenopausal women and it was reported which melatonin supplementation was tolerated; increase biomechanicalproperties with perimenopause, and could restore imbalances in remodeling phase for bone loss prevention. But there is not another investigation to warrant this effect [28].

Melatonin and Bone Physiology

The most important effects of melatonin on bone biology were reported by different researchers during the last years [10]. These studies were made on the basis of evidence for the melatonin of PTH and calcitonin secretion control, demonstrable by the functional and histopathological changes observed in parathyroid glands after pinealectomy [25]. The recent experiments studied the influence of the pineal on serum calcium level. It was saw that inhibition the synthesis of melatonin by exposure of young rats to fluorescent light decrease the serum calcium concentration [21]. This effect was prevented by administration of melatonin) [31]. In addition light induced hypocalcemia can be a result of increased calcium comprehension by bone when serum melatonin levels are decreased after inhibition of its synthesis by fluorescent light [32]. In one study it is shown that when melatonin secretion isdecreasedby administration of adrenoceptor blockers, serum level of calcium dropped [33].

Melatonin & Bone Healing

The bone healing property of melatonin has been investigated by scientists, and they have observed which melatonin prevent from bone fracture evidenced by histomorphometrical, biomechanical, radiological, and protein analyses. The study show that as the bone resorption is necessary for remodeling during bone healing, melatonin impairs bone healing because ofinhibitionof bone resorption by RANKL-mediated osteoclast activation [34]. Latter studies have showed which melatonin has an important effect in bone-healing because of its regulation of bone cells, antioxidant properties, and promotion of angiogenesis actions [35].

Physiologically Bone undergoes remodeling, and for this remodeling bone needs a balance between bone resorption (osteoclasts) and bone formation (osteoblasts) [36]. It needs the interaction between bone cells to product bone mineral homeostasis and strength mid changing environmental influences [37]. These processes have 3 phases: formation, resorption, activation [38]. It has been documented that melatonin regulates bone growth and bone metabolism (such as IGF-I and also calciotropic, parathyroid, thyroid, adrenocortical and gonadal hormones) [39]. In addition melatonin stimulates mineralization of matrix and osteoblast differentiation [40]. Melatonin also regulates the synthesis of collagenic and noncollagenic proteins of bone matrix [41]. Some of scientist's confidence that there is a relationship between serum level of melatonin and bone mass in postmenopausal osteoporosis [34]. There is similar opinion about the effect of melatonin on osteoporosis, bone remolding, and osseointegration of dental implants [38]. Melatonin, with 3 precept actions, modulates bone remodeling:

1) Direct effects on osteoclast and osteoblast actions [41] including: increase the cell proliferation, collagen expression, stimulation the matrix formation and inhibition osteoclasts differentiation) [42].
2), indirect regulates on bone metabolism [43] such as estrogen, calcitonin, and PTH [44].
3) Production of antioxidant for neutralization of osteoclasts superoxide anions that is needed for degradative process. Scientists have been show that melatonin has positive effect on bone healing process because of its regulation of bone cells, antioxidant properties, and promotion of angiogenesis actions [45]. The inflammatory stage of fracture healing is characterized by clot formation and infiltration of inflammatory cells [46]. In this stage, neutrophils produce oxygen free radicals which cause to cell membrane destruction because of lipid peroxidation [47]. This has a negative role on bone healing [48]. Melatonin is a free radical scavenger and antioxidant [42]. Halici, et al. report that melatonin decreases the length of inflammatory stage of fracture healing. So it shows that administration of melatonin is beneficial in antioxidant enzyme activity regulating, and suppressionof the effects of free oxygen radicals thereby accelerating bone formation in bone healing [41]. In the earlystage of bone healing, melatonin encourage the proliferation and differentiation of osteoblast and enhances the type I collagen deposition. It also promotes angiogenesis in callus [44]. The new bone formation is dependent on angiogenesis for provide mineral elements and the migration of osteoprogenitorcells into secluded spaces [46]. In

addition melatonin influences the bone healing during the remolding phase [35]. Administration of melatonin can protect bone tissue from the future fracture [21]. It has established that the bone resorption is an essential requisite for bone remodeling; melatonin impairs remodeling by bone resorption suppressing. It is important note in osteoporotic bone [48]. Melatonin directly acts on the osteoclast that reabsorbs the ECM by free radicals production [41]. Melatonin, due to its antioxidant effect and detoxifying the free radicals, can interfere with this function of the osteoclasts and therefore inhibition of bone resorption; which is enhanced by a reaction of indoleamine osteoclastogenesis [49]. Melatonin can increase bone mass by suppressing of bone resorption. It indicates the osteogenic effect of melatonin [50] and therefore bone grafting in the defect site of bone facilitate healing [34].

No	Researcher	Year	Result
1	Ladizesky, et al. [46]		Melatonin has an effect on bone remodeling, decrease bone loss
2	Halici, et al. [8]		Melatonin decreases the early stage of fracture healing, melatonin is beneficial in suppressing the effects of free oxygen radicals, it regulates antioxidant enzyme activity, it accelerate bone formation
3	Soybir, et al.		Melatonin increases the number of blood vessels in bone healing
4	Yamada, et al.		Melatonin has a positive effect an angiogenesis
5	Ostrowska et al. [42]	2001	Melatonin change the bone metabolism biomarkers, Melatonin has protective significance effect in loss of bone mass
6	Feskanich, et al. [51]		Decreased melatonin serum level increases the risk of bone fractures
7	Uslu, et al. [49]		Melatonin increases trabecular thickness and the trabecular area of vertebra and femur and cortical thickness of femur
8	Guardia et al.		Melatonin increases the inter-thread bone and new bone formation
9	Calvo-Guirado, et al.		Melatonin increases the perimeter of bone that was in direct contact with the treated implants, it increases bone density, it increases new bone formation
10	Radio, et al. [36]		Melatonin inhibits human adult mesenchymal stem cell proliferation
11	Nakade, et al		Melatonin stimulated proliferation of human osteoblasts
12	Roth, et al.		Melatonin has stimulatory effect of bone formation
13	Conconi, et al.	2000	Melatonin has antioxidant properties and has ability to detoxify free radicals
14	Schroeder, et al.	1981	Melatonin inhibits bone resorption
15	PenarrochaDiago, et al.	2005	Melatonin decreases bone mass
16	Cutando, et al. [28]		Melatonin implants increases all parameters of osseointegration: percentage of bone contact, total peri-implant bone, bone interscrew, and the percentage of new bone formation.
17	Sethi, et al. [39]		Melatonin is required for osteoblast differentiation to occur
18	Amstrup, et al.		Melatonin changes osteoclast or osteoblast activity
19	Nakade, et al.	1999	Melatonin enhances also synthesis of collagenic and noncollagenic proteins of bone matrix
20	Sandyk, et al.	1992	Melatonin changes of bone mass
21	Koyama, et al.		Melatonin would increase bone mass
22	Park, et al. [52]		Melatonin promoted differentiation of osteoblast precursor cell line, melatonin causes an increase in levels of markers of bone differentiation and proliferation, including increased synthesis of osteopontin, alkaline phosphatase, procollagen type I c-peptide, and osteocalcin
23	Satomura, et al. [9]		melatonin promoted differentiation of human osteoblastic cells, stimulated the formation of the mineralized matrix

Table 1: There are the finding from studies about melatonin and bone healing.

In the first stage of bone healing, the inflammatory phase is described by ischemia, clot formation and reperfusion injury, also inflammatory cells infiltration [22]. In this stage, neutrophils realize free oxygen radicals which initiate a series of reaction which cause to cell membrane damage because of lipid peroxidation [51]. This may have negative effects on fracture healing.

A study carried out observation of the outcomes of IP use of melatonin for accelerating bone healing. Its authors found which malondialdehyde levels, myeloperoxidase and superoxide dismutase activity in the melatonin group decreased at the first stage of bone healing process compare to the control group [53].

In the proliferative phase, the second phase, cell differentiation, collagen deposition, angiogenesis, and formation of granulation tissue take place [51]. Melatonin enhances the collagen deposition and promotes the proliferation and differentiation osteoblast [22]. Also a recent study reported which melatonin promotes angiogenesis in bone healing process [54]. They observed new capillary buds and increase in the capillary number in melatonin group that were accompanied by increase in length of bone formation [55]. Another researcher reported an increase in capillary number by melatonin applications to wounds in rats [46]. Angiogenesis is important in healing process [53]. Some of scientists suggest which angiogenesis precedes bone formation and osteogenesis [56]. New bone formation dependent on angiogenesis for providing mineral elements and also migration of osteogenic and angiogenic cells into solitary spaces [57]. Remolding stage of bone healingis mediated by growth factors, hormones, cytokines and other elements [58]. One of these hormones is melatonin [59]. It is seems which melatonin, through three principle process, modulates bone metabolism [60]. First, melatonin affects osteoclast and osteoblast actions [61]. Numerous studies report which melatonin can increase pre-osteoblast, osteoblast, and osteoblast-like cell proliferation, and promotes the expression of type I collagen fibers and bone marker proteins like osteopontin, alkaline phosphatase, osteocalcin and bone sialoprotein, and stimulates mineralized matrix formation [62]. In addition melatonin inhibits the osteoclasts differentiation with restriction in the expression of RANK-mRNA and increases in the protein amount of osteo-protegerin and mRNA [53]. Second, melatonin can regulate bone metabolisms via the interaction with different hormones such as, calcitonin, PTH, and estrogen. One study revealed which exogenous estradiol can prolong the effects of melatonin in augmentation of bone remodeling in ovariectomized animals [58]; it shows which estradiol blood levels may be required for melatonin effect on bone [52]. Third, osteoclasts always generate a lot of amount of superoxide anions which contribute to the degradative process [60]. Melatonin is an antioxidant and free-radical scavenger. It can clear the oxygen free radicals and protect osteoblasts and osteocytes from oxidative attacks [52]. Discussion There is little study about the effects of melatonin on bone healing; and most of them are about ovariectomized animals and animals with scoliosis [54]. Most of them accent the positive effects of melatonin on osteoblasts and bone formation and negative effects of melatonin on osteoclasts and bone resorption [22]. The point is that melatonin in low dosage has not these effects and therapeutic dose of melatonin is toxic for body tissues. So the real effects of melatonin in body are unknown. Melatonin has a free radical scavenging ability that reduces lipid peroxidation. In addition It has been reported that melatoninscavenges the hydroxyl radical [22]. The antioxidant property of melatonin derives from its stimulatory effect on glucose-6-phosphate dehydrogenase, glutathione reductase and SOD and its inhibitory effect on NO synthase. Also melatonin can effect on cell membrane, by making it more resistant to oxidative attacks [56]. Some studies suggest that melatonin can effects bone tissue metabolism and pinealectomy in rat can increase the collagen degradation marker as a bone resorption marker [63]. Melatonin can lead to increase of bone mineral content thereby inhibiting bone degradation [51]. Melatonin stimulates production of Type I Collagen in osteoblasts [63]. It can change the arrangement of the collagen matrix in bone tissue, by increasing its capacity to resist fracturing [57]. That melatonin has a direct effect on bone was indicated by the exhibition which it inhibited calcium uptake in bone samples of rats treated with pharmacologic amounts of corticosterone [56].

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