

Melatonin can restore the density of bone decreased by hyperthyroidism-induced osteoporosis

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ABSTRACT

Background: Hyperthyroidism is accompanied by increased rates of bone formation and resorption. Melatonin through its free radical scavenging and antioxidant properties, impairs osteoclast activity and bone resorption in hyperthyroid state.

Aim: To study the effect of melatonin on bone density decreased during hyperthyroidism.

Duration of study: 01 November to 30th of January, 2014-15.

Study design: Randomized Controlled Trial.

Place of study: Anatomy department at BMSI, JPMC, Karachi.

Methods: Ninety healthy adult albino rats were included in the study and divided equally into 3 groups for 12 weeks. Group-A was taken as control. Group-B received levothyroxine orally, daily in a dose of 8 µgm /100 g BW for 12 weeks to induce experimental hyperthyroidism. Group C was given levothyroxine orally in the above mentioned dose as well as melatonin in drinking water daily in a dose of 10 mg/100 g BW.

Results: Melatonin significantly restored the thickness of bone cortex in the shaft of femur in group B without affecting the levels of TSH in hyperthyroid state.

Conclusion: Melatonin can promote bone formation and prevent bone resorption during hyperthyroidism.

Keywords: Melatonin, Hyperthyroidism, levothyroxine, BMD, Albino rats.

INTRODUCTION

Thyroid hormones are essential for the normal growth and maturation of skeleton¹. Hyperthyroidism is accompanied by increased rates of bone formation and resorption². Thyrotoxicosis speeds up bone remodelling which is the reason why it leads to osteoporosis³. It is very rare to see osteoclasts in bone under physiological conditions, but their number increase in many pathological states, which results in decrease in the density of bone⁴.

TSH inhibits osteoclast formation and in the hyperthyroid state, where TSH is severely suppressed, osteoclast formation is enhanced⁵. The basal metabolic rate of the body increases during hyperthyroidism which leads to an increase in the production of reactive oxygen species causing obvious changes in antioxidants. This is the reason why hyperthyroidism causes oxidative stress⁶.

Melatonin is a hormone secreted endogenously by the pineal gland. The suprachiasmatic nucleus regulates its secretion and so does the light-dark cycle⁷. Apart from its powerful antioxidant properties,

melatonin has recently attracted the interest of various investigators as a multifunctional molecule⁸. Melatonin plays an important role in many aspects of physiology of living things by acting on various cells of the body through its two types of G protein coupled receptors MT1 and MT2⁹. In fact, it is because of the activation of these receptors that many physiological effects of melatonin occur. Other effects of melatonin are due to its anti-oxidant effects. Its role in the protection of nuclear and mitochondrial DNA cannot be underestimated and has led researchers to explore this hormone in depth in order to heal many diseases which are due to DNA damage¹⁰.

Currently, the role of melatonin in the proliferation and development of hard tissues, including bone and tooth, is the main topic of interest. It is still under investigations how melatonin affects the composition of bone in conditions which leads to bone loss. The role of melatonin has been investigated in bone remodelling, osteoporosis and dentine formation. Osteoporosis is a prolonged structural deterioration of the skeletal system, usually associated with age, and with a major prevalence in women¹¹. The World Health Organization (WHO) defines osteoporosis as bone mineral density (BMD) 2.5 or more standard deviations below that of a young adult at any site.

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The present study was designed to observe the deteriorating effects of hyperthyroidism on bone architecture and density and significant role of melatonin as an antioxidant and a bone conserving drug to treatment regime in order to combat damage induced by free radicals and overcome osteoporosis.

MATERIALS AND METHODS

This study was conducted in the Department of Anatomy, Basic medical sciences institute, Karachi for a period of 12 weeks on 90 albino rats obtained from the animal house and divided randomly into 3 groups. Group A served as control. Group-B received levothyroxine orally, daily in a dose of 8µgm /100 g BW for 12 weeks to induce experimental hyperthyroidism. Group C was given levothyroxine orally in the above mentioned dose as well as melatonin in drinking water daily in a dose of 10mg/100g BW.

They were housed in well labelled plastic cages in the experimental room of Animal House and maintained on balanced laboratory diet. Rats were kept under observation for a week to acclimatize them to their new environment. Food and water were supplied ad libitum. The animals were sacrificed at the end of their respective treatment. Blood samples were collected from the cardiac region immediately after sacrifice to carry out serum TSH for biochemical analysis.

Right femurs were separated, carefully cleaned and then fixed in 10% formalin until analysis. The bone was decalcified with a mixture of 10% formic acid and hydrochloric acid solution for 7 days. After decalcification, sections were taken longitudinally and transversely from bone. All the tissues were processed overnight, embedded in paraffin and sectioned at a thickness of 15 micrometer. The sections were stained with hematoxylin and eosin. Randomly selected areas from shaft of the femur were measured for bone cortex thickness by morphometry of all the rats. Serum TSH by ELISA method was also estimated.

RESULTS

Table-1: Mean values of morphometric measurements of cortex of femur in all the 3 groups;

Groups	Bone cortex thickness (µm)
A	388.52±40.21
B	220.16±29.21*
C	334.82±28.72*

*Statistically significant at $p < 0.001$ as compared to control group.

The table above shows a significant ($p < 0.05$) effect of levothyroxine in reducing cortical thickness in group

B and that of melatonin in restoring cortical thickness in group C rats.

Table2: Change in mean serum TSH concentration in all 3 groups;

Groups	Treatment Received	Serum TSH(µIU/ml)
A	Control	130±2.10
B	levothyroxine	98±1.28*
C	levothyroxine + Melatonin	101±1.9

*Statistically significant at $p < 0.05$ as compared to control group.

Serum TSH was significantly decreased in both group B and C, indicating no significant effect of melatonin in restoring thyroid hormone levels.

DISCUSSION

This study highlighted the positive role of melatonin on the density of bone reduced during hyperthyroid state. It was observed that melatonin prevented bone loss without affecting the serum levels of TSH. It is likely that melatonin promotes the formation of bone by preventing the process of bone resorption. There are several mechanisms which can justify and elaborate this action of melatonin. It is stated and worked upon that melatonin seems to promote bone formation and prevent bone resorption via several mechanisms which include the increase in the osteoblastic activity and differentiation, as well as the reduction in osteoclastic differentiation and activity. It has also been studied that melatonin destroys the free radicals which are responsible for resorption of bone¹².

It has been demonstrated via several experiments in vitro that osteoclasts produce free radicals which are responsible for the production of degradation and resorption of bone¹³. Since melatonin has the capability of destroying free radicals and activating anti-oxidative enzymes, this can be a factor which leads to the reduction in the activity of osteoclasts.

The hormone melatonin is formed in the brain's pineal gland where it regulates the sleep wake cycle. There is evidence that large amounts of melatonin are also produced within the bone¹⁴. In spite of having diverse functions in the body, which includes its antitumor, antiangiogenic, and antioxidant effects, the mechanism of melatonin by which it influences the activities of bone still remains obscure.

Melatonin, perhaps through destroying free radicals and working as an antioxidant, impairs osteoclast activity and bone resorption during hyperthyroidism¹⁵. As its concentration in the serum is not adequate to overcome bone loss and oxidative

damage, therefore, additional supplementation of exogenous melatonin is necessary to preserve the density and architecture of bone and preserve and decrease the levels of oxidative stress at the cellular level.

Apart from its beneficial use during hyperthyroidism, melatonin can also be used as a supplement in the postmenopausal women who suffer from osteoporosis. It can be used as a supplement along with estrogen, to overcome bone loss.

CONCLUSION

Melatonin can promote bone formation and prevent bone resorption during hyperthyroidism.

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