

ARTICLE

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## Efficacy of Melatonin on Neuro-Psychiatric Symptoms of Elderly Patients with Hypothyroidism

### ABSTRACT

**Aim:** In this study, it was aimed to investigate of the clinical efficacy of melatonin treatment on neuropsychiatric symptoms in elderly patients with hypothyroidism.

**Method:** The study was conducted on 51 patients with hypothyroidism. The patients' anxiety, depressive symptoms and sleep disturbance were recorded with the Hospital Anxiety and Depression Scale (HADS). The Patients were randomized into two groups. The first group of patients (25 patients) received standard replacement therapy with L-thyroxine and symptomatic therapy for 1 month. The second group of patients (26) received melatonin at a dose of 15 mg per night for 1 month (combination therapy) along with L-thyroxine.

**Results:** There was a significant decrease in TSH levels after therapy in both groups. The decrease was more in the group who received combination therapy ( $82,2 \pm 1,5\%$  versus  $66,1 \pm 2,4\%$ , respectively). Depressive state was significantly reduced only in the combination therapy group ( $10,9 \pm 0,9$  points versus  $6,9 \pm 0,5$  points). Furthermore, in patients receiving melatonin there was a significant reduction in subclinical depression ( $13,2 \pm 3,4\%$  versus  $7,7 \pm 1,1\%$ ,  $p < 0,05$ ).

**Conclusion:** Addition of melatonin to the standard therapy is effective in controlling depressive symptoms in patients with hypothyroidism living in Kazakhstan

**Keywords:** Elderly, Hypothyroidism, Melatonin

## Melatonin Tedavisinin Yaşlı Hipotiroidili Hastaların Nöro-Psikiyatrik Semptomları Üzerindeki Etkinliği

### ÖZET

**Amaç:** Bu çalışmanın amacı melatonin tedavisinin yaşlı hipotiroidili hastaların nöro-psikiyatrik semptomları üzerindeki etkinliğini araştırmaktır.

**Metot:** Hipotiroidili 51 hasta çalışmaya alındı. Hastaların depresyon ve anksiyete skorları ve uyku bozukluğu derecesi "Hastane Anksiyete Depresyon Skalası" (HADS) skalası ile değerlendirildi. Hastalar bir ay süreyle L-tiroksin ve melatonin+ L-tiroksin tedavilerine randomize edildiler.

**Bulgular:** Tedavi sonrası kombinasyon tedavisi alan grupta daha fazla olmak üzere her 2 grupta TSH seviyeleri geriledi ( $82,2 \pm 1,5'$  ye karşılık  $66,1 \pm 2,4$ ). Depressif durum kombinasyon tedavisi alan grupta anlamlı olarak azaldı ( $10,9 \pm 0,9$  puana karşılık  $6,9 \pm 0,5$  puan). Ayrıca kombinasyon tedavisi alan grupta subklinik depresyon oranı azaldı ( $13,2 \pm 3,4'$  ye karşılık  $7,7 \pm 1,1$ )

**Sonuç:** Kazakistan'da yaşayan hipotiroidili hastalarda standart tedaviye melatonin eklenmesi hastaların depressif semptomlarını kontrol altına almada etkilidir.

**Anahtar kelimeler:** Yaşlı, Hipotiroidi, Melatonin.

## INTRODUCTION

It is known that in hypothyroidism due to deficiency of thyroid hormones causes disturbed morphogenesis of the brain, slowing the formation of synapses, proliferation and differentiation of glomerular cells, impaired myelination (1,2). Slowing of cognitive processes in hypothyroidism is due to the reduction of metabolic processes: a decrease of cerebral blood flow, reducing the consumption of oxygen and glucose, as well as increasing resistance in the vessels of the brain. Impaired function of the peripheral nervous system shows decline in the rate of nervous excitement, the development of polyneuropathy, paresthesia, and loss of sensitivity (2).

In recent years, diffuse neuroendocrine system (DNES) is the subject of much research (3, 4). Functionally part of the DNES are melatonin-producing neuroendocrine cells involved in the universal system of adaptation and the maintenance of homeostasis (3). For many years, melatonin is considered only as a hormone of the pineal gland. Now it is proved that its source in the body are ekstrapineal tissues such as the retina, the cerebellum, the mucous membrane of the gastrointestinal tract and respiratory tract, liver, kidneys, adrenals, thymus, thyroid gland, pancreas, ovary, carotid body, placenta, endometrium, the mast cells, natural killer cells, eosinophils, platelets and endothelial cells (4).

In the experimental work of Bondarenko and Gevorgyan, a direct stimulatory effect of melatonin on the activity of the thyroid gland of old rats was demonstrated (5). However, the effect of melatonin in patients with hypothyroidism has not been studied yet. Therefore, the aim of the study was to evaluate the clinical efficacy of melatonin in patients with hypothyroidism.

## MATERIALS AND METHODS

The study was conducted on 51 patients with hypothyroidism (often on a background of autoimmune thyroiditis) with an age range of 25 to 63 years. The patients' anxiety, depressive symptoms and sleep disturbance were recorded. Blood levels of thyroid hormones was determined by ELISA method using commercially available kits (BEST, Russia). The normal reference range of thyroid stimulating hormone (TSH) was 0,17-4,05 mIU /L, and was 10-25pmol for free T<sub>4</sub>. Analysis of the nervous system included interpretation of Hospital Anxiety and Depression Scale (HADS - hospital of alarm and depression scale) using subscales; - A - anxiety subscale, D - depression subscale, with three allocated range: 0-7 - "normal", 8 - 10 - "subclinical severe anxiety and depression, 11 and above - "clinically significant anxiety and depression, respectively. The samples were divided into 2 groups. The first group of patients with overt hypothyroidism (25 patients) received standard replacement therapy with L-thyroxine and

symptomatic therapy for 1 month. The second group of patients with overt hypothyroidism (26) received melatonin at a dose of 15 mg per night for 1 month (combination therapy) along with L-thyroxine. The study was conducted according to standards of good clinical practice and the resolution of the local ethics committee. Local ethics committee approved the study and all the patients signed an informed consent.

**Statistical analysis:** Statistical analysis of the results was done by a computer program SPSS to analyze the reliability of the Student t test.

## RESULTS

Age of the patients with overt hypothyroidism was 45,9±1,5 years. Duration of disease ranged from 1 to 3 years, with an average of 5,2±0,9 years. All patients with hypothyroidism had sleep disturbances, manifested in the brevity of sleep, interrupted sleep and anxiety.

Thyroid hormone levels of patients who received L-thyroxine or combination therapy was similar. There was a significant decrease in TSH levels after therapy in both groups. However, the decrease was more in the group who received combination therapy. (Percent reduction 82,2±1,5% versus 66,1±2,4%, respectively) (Table 1) Free T<sub>4</sub>, on the other hand, increased significantly again with a more stronger peak in the combination group (Percent change 56,8 ± 2,4% versus 39,3 ± 2,6%, respectively).

The assessment of HADS performance scales showed that 63,5±0,7% of the patients had pronounced depression and a pronounced anxiety was observed in 38,5±0,6% of the cohort. A combined pronounced anxiety-depressive syndrome was detected in 28 patients.

Pre-treatment anxiety was equal to 11,1±0,6 points in the L-thyroxine therapy group and 12,3±1,2 points in the combination therapy group (Table 2). Anxiety was observed in patients with hypothyroidism in the form of panic, tension and fear in disguise slowness of facial expressions and speech. Subclinical anxiety was noted in 26,7±8,1% and 27,4±5,2% of patients of patients before treatment in groups 1 and 2, respectively. Overt anxiety was detected in 53,1±7,0% of patients in group 1 and in 50,0±8,0% of patients in group 2. Pre-treatment depression was 10,2 ± 0,6 points in group 1 and 10,9±0,9 points in group 2. Clinically-defined depressive manifestations in patients with hypothyroidism manifested slowness of thinking, decreased motor activity, drowsiness, loss of sense of enjoyment of life. The frequency of subclinical depression was shown in Table 2. Anxiety and depression points and frequency did not differ among the groups before therapy. After the treatment, there was a significant reduction in anxiety, including subclinical anxiety in both groups. Depressive state was significantly reduced

only in the combination therapy group ( $10,9 \pm 0,9$  points versus  $6,9 \pm 0,5$  points ( $p < 0,05$ ). Furthermore, in patients receiving melatonin there

was a significant reduction in subclinical depression ( $13,2 \pm 3,4\%$  versus  $7,7 \pm 1,1\%$ ,  $p < 0,05$ ).

Table 1. The evolution of the hormones of thyroid status in patients with hypothyroidism

Total	TSH (mIU/mL)		Free T <sub>4</sub> (pg/mL)	
	Before	After	Before	After
	treatment	treatment	treatment	treatment
L-thyroxine + Melatonin Treatment (n=26)	25.2±9.5	4.5±1.1*	7.9±1.2	18.3±2.2*
L-thyroxin (n=25)	24.5±5.1	8.2±3.2	8.6±2.4	14.2±3.2
* p < 0,05				

Table 2. Performance scales of HADS in patients with manifest hypothyroidism

Groups, indicators	L-thyroxine (n=25)		L-thyroxine + Melatonin (n=26)	
	Before treatment	After treatment	Before treatment	After treatment
Disturbing condition in points	11.1±0.6	8.2±0.3*	12.3±1.2	7.1±0.3*
Depression in points	10.2±0.6	8.6±0.4	10.9±0.9	6.9±0.5*
Subclinical disturbing condition, %	26.7±8.1	12.0±3.5*	27.4±5.2	11.5±4.1*
The expressed disturbing condition, %	53.1±7.0	44.0±8.0	50.0±8.0	41.1±7.2
Subclinical depressive condition, in %	13.0±4.2	12.0±2.5	13.2±3.4	7.7±1.1*
The expressed depression, in %	34.4±8.8	32.0±7.6	34.6±4.3	30.7±6.9
* p < 0,05				

**DISCUSSION**

The results of the present study showed that addition of melatonin to the standard therapy is effective in controlling depressive symptoms in patients with hypothyroidism living in Kazakhstan. Melatonin is secreted in a daily manner (circadian rhythm) from the pineal gland in humans. The melatonin concentrations were positively correlated with TSH levels in hypothyroidism, and negatively correlated with T3 in hyperthyroidism. Although the exact mechanism is not known there may be a hypothalamo- hypophysial interaction indicating melatonin-induced changes in secretion of thyroid hormones, gonadal hormones, and hypothalamic hormones. Previously published data suggest that in

the female hamster melatonin injections resulted in significant depression of serum TSH compared to saline-injected controls (5,6).

However, the effect has never been studied extensively in humans. For the first time in the English literature we showed that oral melatonin therapy is also effective in decreasing TSH levels and depression scores in humans.

**As a conclusion,** we suggested that the combination of melatonin with the standard L-thyroxine therapy may have beneficial effects on removing anxiety and depression in patients with hypothyroidism

**REFERENCES**

1. Berbel P, Guadano-Ferraz A, Angulo A. Role of thyroid hormones in the maturation of interhemispheric connection in rats. *Behav Brain Res.* 1994;64(1-2):9-14.
2. Pal'tsev MA, Kvetnoĭ IM, Poliakova VO, Kvetnaia TV, Trofimov AV. [Neuroimmunoendocrine mechanisms of aging]. *Adv Gerontol.* 2009;22(1):24-36. Review. [Russian].
3. Kvetnoy IM, Hernández-Yago J, Hernández JM, Kvetnaia TV, Reiter RJ, Khavinson VK. Diffuse neuroendocrine system and mitochondrial diseases: molecular and cellular bases of pathogenesis, new approaches to diagnosis and therapy. *Neuro Endocrinol Lett.* 2000;21(2):83-99.
4. Anisimov VN, Bondarenko LA, Khavinson VK. Effect of pineal peptide preparation (epithalamin) on life span and pineal and serum melatonin level in old rats. *Ann N Y Acad Sci.* 1992 Dec 26;673:53-7.
5. Bondarenko LA, Gevorkyan AR. The Influence Of A Course Injection Of Melatonin On The Hormonal Activity Of The Hypophyseal-Thyroid System In Old Rats With Age-Related Hypothyroidism. *Буковинський медичний вісник. Buk. Med. Herald.* 2009;13(4): 38-40.
6. Vriend J, Wasserman RA. Effects of Afternoon Injections of Melatonin in Hypothyroid Male Syrian Hamsters. *Neuroendocrinology* 1986;42(6):498-503.