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Melatonin Serum Levels in Rheumatoid Arthritis

Romatoid Artritte Serum Melatonin Düzeyleri

Tuba BAYKAL, Kazım ŞENEL, Meltem ALKAN MELİKOĞLU, Akın ERDAL, Hamit Hakan ALP*, Mahir UĞUR

Ataturk University School of Medicine, Department of Physical Medicine and Rehabilitation, Erzurum, Turkey

** Ataturk University School of Medicine, Department of Biochemistry, Erzurum, Turkey*

Summary

Objective: Recent studies suggest that endogenous melatonin (MLT) production might play a role in the etiology of rheumatoid arthritis (RA). However, the role of MLT in RA pathogenesis remains unclear. This study was performed to determine MLT serum levels in RA patients.
Materials and Methods: Twenty nine patients with RA and in 25 age- and sex-matched healthy controls were included in our study. Blood samples of the participants collected at 8AM. MLT was measured by enzyme-linked immunosorbent assay (ELISA). The MLT levels of the patients with RA were compared with healthy age- and sex-matched controls. The Mann-Whitney U-test was used to compare the data between the two groups.
Results: MLT concentrations were significantly higher in RA patients than in the controls ($p<0.05$).
Conclusion: Our results suggest that the higher blood concentrations of MLT in RA patients, especially in the early morning, may help to explain the morning stiffness and joint swelling. *Turk J Phys Med Rehab 2013;59:42-4.*
Key Words: Rheumatoid arthritis, melatonin

Özet

Amaç: Son çalışmalar endojen melatonin (MLT) üretiminin romatoid artrit (RA) etyolojisinde rol oynayabileceğini ileri sürmektedir. Ancak MLT'nin RA patogenezindeki rolü açık değildir. Bu çalışma RA'lı hastalarda MLT düzeylerini belirlemek için düzenlenmiştir.
Gereç ve Yöntem: Çalışmamıza 29 RA hastası ile yaş ve cins olarak eşleştirilmiş 25 sağlıklı kontrol dahil edildi. Katılımcıların kan örnekleri sabah 8:00'da alındı. MLT enzyme-linked immunosorbent assay (ELISA) yöntemiyle ölçüldü. RA hastalarının MLT düzeyleri yaş ve cins olarak eşleştirilmiş kontroller ile karşılaştırıldı. Gruplar arasındaki verilerin karşılaştırılmasında Mann-Whitney U test kullanıldı.
Bulgular: MLT düzeyleri RA hastalarında kontrol grubundan anlamlı olarak daha yüksekti ($p<0,05$).
Sonuç: Sonuçlarımız RA hastalarındaki özellikle sabah erken dönemdeki yüksek MLT düzeylerinin sabah tutukluğu ve eklem şişliğini açıklamada yardımcı olabileceğini desteklemektedir. *Türk Fiz Tıp Rehab Derg 2013;59:42-4*.
Anahtar Kelimeler: Romatoid artrit, melatonin

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory rheumatic disease with unknown etiology (1). The symptoms of the patients with RA demonstrate a circadian rhythm with joint stiffness and pain especially in the morning (2). Several studies have reported that increased concentration of oxidative stress have been found in RA patients. It has been suggested that oxidant status may be associated with increased disease activity (3-5).

Melatonin (MLT) was discovered as an antioxidant in 1993, thousand of investigations have confirmed the anti oxidative actions of MLT (6). It is also well established that MLT is one of the most powerful, endogenous free radical scavengers (3). The clinical studies support that MLT has antioxidant, immunomodulatory and anti-inflammatory functions (1,7). Evidence suggesting the involvement of MLT in RA has been published (1,2). However, the role of MLT in RA pathogenesis remains unclear (8).

In previously studies evaluating MLT concentrations in RA patients were found lower serum levels of MLT. It has been suggested that there was the link between the antioxidant activity loss of MLT hormone and disease activity (3,9). On the contrary, recent studies indicate that MLT production in patients with RA seems to be greater than in healthy controls (2,10). We, therefore, evaluated the serum MLT levels, and discussed the role of MLT in patients with RA.

Address for Correspondence:/Yazışma Adresi: Kazım Şenel MD, Ataturk University School of Medicine, Department of Physical Medicine and Rehabilitation, Erzurum, Turkey
Phone: +90 442 233 11 22 E-mail: kazimsenel@gmail.com
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Methods

Serum levels of MLT were evaluated in 29 patients with RA and in 25 healthy control subjects in the division of Rheumatology of Ataturk University. The diagnosis of RA fulfilled the American College Rheumatology (ACR) criteria. Each patient was diagnosed by a same physician. All patients had active disease. Each patient was receiving medications, either oral prednisolone or a disease-modifying anti-rheumatic drug. Control subjects consisted of healthy subjects. The age and sex of controls were matched for those of RA patients. There was no significant difference between the groups regarding mean age. Controls had no clinical evidence of rheumatic disease or any other disorders. All studies were carried out according to the standards set by the Declaration of Helsinki.

Blood samples were obtained at 8AM. The concentration of MLT in plasma collected in EDTA-containing tubes was measured by DRG melatonin enzyme-linked immunosorbent assay (ELISA) (EIA-1431).

10 ml blood sample was obtained through venipuncture from each patient. This sample was taken by a phlebotomist into heparin/EDTA tubes and was centrifuged at 3000 x g and stored at -80°C until biochemical analysis.

Statistical Analysis

Statistical analysis was carried out using the Mann-Whitney U-test. A probability (p) value of less than 0.05 was considered statistically significant.

Results

In the present study, the mean age ± standard deviation of mean in years in both RA patients and controls were 49.4±0.8 and 47.8±0.7, respectively. The numbers of female and male RA patients were 20 and 9, respectively, and those in controls were 17 and 8, respectively (Table 1). There was no statistically significant difference between RA patients and controls in age and sex.

Demographics and clinical features of patients are given in Table 1.

Serum levels of MLT in RA patients and controls are given in Table 2. RA patients had higher MLT concentrations at 8AM than in controls, at 15.40±10.12, 10.03±5.85 pg/ml ($p<0.05$).

Table 1. Demographics and clinical features in RA patients and controls.

	Controls (n=25)	Patients (n=29)
Age (mean±SD)	47.8±0.7	49.4±0.8
Female/male	17/8	20/9
Disease duration (mean±SD.yr)		6.4±0.6
RF (+) (%)		20

Table 2: Serum Levels of MLT in controls and RA patients.

Group	MLT concentrations (pg/ml)
Control	10.03±5.85
RA	15.40±10.12*

* $p<0.05$

Discussion

Since MLT is a part of many processes, it is considered to possibly be involved in the ethiopathogenesis of various conditions. In order to establish the role of MLT in disease prevention and or treatment, scientific evidence is being collected in experimental and clinical studies (11,12).

MLT is a neurohormone that in recent years has attracted great attention. Due to its wide-spectrum of properties, it has been suggested to be effective in the etiology and treatment of many diseases. It has actions on the immune diseases and on the immune system and also has antioxidant features. These draw interest to this hormone's role in chronic inflammatory diseases. In addition, detection of a correlation between the circadian release of MLT and rhythmic symptoms and signs of RA patients has lead to addressing its involvement in rheumatic diseases. RA shows rhythmic variation in clinical signs and symptoms depending on the biological clock (13). Preclinical and clinical evidences indicate an impulsive role of MLT in RA (14-16). MLT concentrations are increased in the serums of RA patients and it can be effective in inflamed joints either locally or systemically. The circadian release of MLT and its nocturnal peak are correlated with the daily rhythm of RA symptoms. MLT serum levels are significantly higher in RA patients when compared to controls between 8AM and 8PM. Maximal inflammation is observed between midnight and 8AM, and joint stiffness and pain complaints are more intense during morning hours (13-15).

Recently, MLT is found to be involved in the mechanisms of an opposite response to the cortisol effects in RA patients (13). Generally, MLT shows an immune-strengthening effect. It activates T lymphocytes, monocytes, NK cells and even neutrophils activate antibody-dependent cytotoxicity and increased antibody response. Increasing the synthesis of pro-inflammatory cytokines and nitric acid is a feature that has also been demonstrated (14,17). Cytokines reach a peak during the night and early morning, when cortisol is at its lowest level and MLT is at its highest. IL-l, IL-2, IL-6, IL-12 and tumour necrosis factor (TNF) are considered to be functional, MLT seems to play a role in stimulating a more active inflammatory response during the night. Moreover, MLT has been detected at high levels in the synovial fluids of RA patients (16,18-20). Regarding these results, the inhibition of MLT synthesis or administration of its antagonists may hold a therapeutic effect for RA (13,21).

A number of studies have addressed the anti-inflammatory and immunoregulatory features of MLT. West and Oosthuizen (9) initially found that the daytime MLT concentration was significantly lower in untreated RA patients. In the second part of their study, healthy individuals received indomethacin at a dose 100 mg/day, leading to a reduction in MLT levels. In view of these findings, it could be considered that MLT and indomethacin, which are structurally similar within the body, retain a synergistic effect, and that MLT is able to simultaneously perform an anti-inflammatory activity. Owing to its antioxidant and anti-inflammatory properties (3,9), Forrest et al. (3) investigated the use of MLT in the treatment of 75 RA patients.

As a result, MLT shows a slowly developing anti-oxidant profile in patients with arthritis and increased the concentrations of some inflammatory indicators. By experimentally inducing arthritis, Cardinali et al. (22) compared the inflammatory and

immune responses elicited by physiological and pharmacological doses of MLT; while a recovering inflammatory response to low doses was observed at a lower rate in pinealectomized rats, however, under high doses, both inflammatory and immune responses were increased.

The investigation of a genetic correlation between MLT and RA has been performed by Ha et al. in Korea (1). It was verified that MLT receptor type, 1B single-nucleotide polymorphism was related to the presence of rheumatoid factor in RA patients.

MLT, cortisol, and cytokine levels in RA patients were measured in Northern Europe (Estonia) and Southern Europe (Italy). MLT concentrations were higher and reached an earlier peak in RA patients from Estonia (10).

In previous research, the macrophages infiltrating the synovial fluid of RA patients were found specific MLT bindings sites. In addition, MLT were also determined at high concentrations in the synovial fluid. However, administration of MLT has been accused of flaring up experimentally induced arthritis in mice (3,23,24).

Experimental studies showed that there are MLT receptors on synovial macrophages (3,18,25). Consequently, it has been suggested that the higher MLT concentrations may help to explain the morning stiffness and joint swelling in arthritic patients (3,16,19).

In the present study, we evaluated the serum levels of MLT in RA patients. We found that MLT concentrations were significantly higher in RA patients than in controls. The increased levels of MLT may have been a compensatory response to the inflammation of RA. These findings suggest that MLT might play a promoting role in RA. In addition, we suggest that inhibition of MLT synthesis and action by specific antagonist might be of therapeutic value. The MLT-RA relationship might explain why clinical symptoms of rheumatoid synovitis are more evident in the early morning.

As a result, all potential effects, advantages, and risks of MLT have not been ascertained yet. Further studies are needed to determine the possible role of MLT in patients with RA.

Conflict of Interest

Authors reported no conflicts of interest.

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