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Original article

Rheumatoid arthritis patients have early chronotype that does not associate with disease activity.

Pacientes com artrite reumatoide têm cronotipo precoce que não se associa à atividade da doença.

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ABSTRACT

Background: Chronotypes refers to one's preferred schedule for sleep and wakefulness. It is closely linked to circadian rhythm that regulates hormone and cytokines release. The circadian rhythm is altered in several immune mediated diseases.

Objective: To study chronotypes in rheumatoid arthritis (RA) patients and their possible relationship with disease activity.

Methods: Cross-sectional study with 77 RA patients and 79 controls. Patients and controls answered the Morning-Evening Questionnaire Self-Assessment Version (MEQ-SA) questionnaire that classifies chronotypes in morning types, evening types and intermediated. Data on disease activity: DAS28 (Disease Activity Index using 28 joints)-ESR (erythrocyte sedimentation rate), DAS28-CRP (C reactive protein), SDAI (Simplified Disease Activity Index), and CDAI (Clinical Disease Activity Index) were collected in RA patients.

Results: In the RA sample, 55 (71.4%) were classified as morning types; 19 (24.6%) as intermediate and 3 (3.8%) as evening types. In the control group 33 (41.7%) were classified as morning types; 40 (50.6%) in intermediated and 6 (7.5%) in the evening type; p=0.0009. No correlation of values of MEQ-SA with disease activity indexes were found (all with p>0.05).

Conclusion: RA patients had earlier chronotype than controls but disease activity did not have influence on this preference.

Key words: Rheumatoid arthritis. Chronotype. Disease activity. Inflammation.

RESUMO:

Introdução: Cronotipos referem-se ao horário preferido de uma pessoa para dormir e acordar. Está intimamente ligado ao ritmo circadiano que regula a liberação de hormônios e citocinas. O ritmo circadiano está alterado em várias doenças imunomediadas.

Objetivo: Estudar cronotipos em pacientes com artrite reumatoide (AR) e sua possível relação com a atividade da doença.

Métodos: Estudo transversal com 77 pacientes com AR e 79 controles. Pacientes e controles responderam ao questionário *Morning-Evening Questionnaire Self-Assessment Version* (MEQ-SA) que classifica os cronotipos em tipos matutino, noturno e intermediário. Dados sobre a atividade da doença: DAS28 (Índice de Atividade da Doença usando 28 articulações) -ESR (velocidade de hemossedimentação), DAS28-CRP (proteína C reativa), SDAI (Índice de Atividade da Doença Simplificado) e CDAI (Índice de Atividade da Doença Clínica) foram coletados em pacientes com AR.

Resultados: Na amostra de AR, 55 (71,4%) foram classificados como matutinos; 19 (24,6%) como intermediários e 3 (3,8%) como tipos noturnos. No grupo controle, 33 (41,7%) foram classificados como matutinos; 40 (50,6%) no tipo intermediário e 6 (7,5%) no noturno; p=0,0009. Não foi encontrada correlação dos valores do MEQ-SA com os índices de atividade da doença (todos com p>0,05).

Conclusão: Os pacientes com AR apresentaram cronotipo mais precoce do que os controles, mas a atividade da doença não influenciou essa preferência.

Palavras-chave: Artrite reumatoide. Cronotipo. Atividade da doença. Inflamação.

Introduction

The immune system functioning is subject to individuals' circadian rhythm[1]. Circadian rhythm refers to a 24-hours cycles that allow the physiological processes to be optimized by regulating the sleep-wake cycles, hormone release, eating habits, and other functions [2]. It is directed by the suprachiasmatic nucleus in the hypothalamus, that communicates with peripheral cells through hormonal and neuronal connections [2,3]. The observable behaviors influenced by the intrinsic circadian rhythm, which dictate one's preferred schedule for sleep and wakefulness, are referred to as chronotype [4].

The autoimmune diseases may be affected by the body clock in at least two ways: 1 - through its influence in their pathophysiologic process; 2 - in the expression of their symptoms [5].

Pro-inflammatory cytokines are linked to the circadian rhythm. Increased sleepiness during infections episodes, that are seen as beneficial, associates with TNF alpha, IL-2 and interferon γ production [6,7]. LPS-dependent secretion of TNF-α is higher at night compared to day and it is further boosted by melatonin [5]. Animal models with autoimmune diseases such as rheumatoid arthritis, RA [1], psoriasis [8]; inflammatory bowel disease [9], etc., have more severe inflammatory phenotypes when the circadian rhythm is disrupted. Concerning disease's clinical expression, the occurrence of morning pain and stiffness in inflammatory arthritis in parallel with pro-inflammatory cytokine and hormone levels fluctuations is well recognized[10].

In RA some interesting observations about influence of circadian rhythm/chronotype have been done. Disturbances in the hypothalamic-pituitary-adrenal axis, reflected in

altered circadian secretion of cortisol, melatonin, interleukin (IL) -6, have been documented on this disease[11]. Neeck et al.[12] reported that in patients with RA, the cortisol levels fluctuated during the day based on the disease activity, being reduced in severe case. Sulli et al.[13] found an altered temporal profile of melatonin in RA patients, with a more rapid increase at the start of the night and with an earlier peak than in healthy controls. Moreover, disruption of clock genes function such as BMAL1 (Brain and Muscle ARNT-like 1), CLOCK (Circadian Locomotor Output Cycles Kaput) Period (PER1, PER2, PER3) and Cryptochrome (CRY1, CRY2) that are part of the circadian rhythm regulatory system, have been linked to development and progression of RA [14]. Curiously, Butler et al.[2] have reported that individuals with morning chronotypes working night shifts had higher probabilities of developing RA when compared to day workers.

Taking into account the mutual influence of the inflammatory process and circadian rhythm it is possible to hypothesized that in RA the inflammatory process may be linked to patient's chronotype.

Herein, we studied RA patients chronotypes comparing them with controls and the possible relationship of their chronotypes with disease activity.

Methods

This is a cross-sectional study approved by the institutional Committee of Ethics in Research (CAAE: 69974123.6.0000.0103) under protocol 6.120.525 with a convenience sample of RA patients from a single tertiary center that cares for patients from the Public Health System. To be included patients should fulfilled at least six points of classification criteria for RA from EULAR/ACR [15] and be older than 18 years of age. Patients using sleep inducing medications, associated fibromyalgia and other inflammatory comorbidities were excluded. Inclusions were done according to consultation order and willingness to participate in the study. Data collection included:

A) Epidemiological and clinical data: sex, age, tobacco and alcohol use, age at diagnosis, presence of rheumatoid factor, DAS28 (Disease activity score using 28 joints) -CRP (C reactive protein), DAS28 -ESR (erythrocyte sedimentation rate), SDAI (Simplified Disease Activity Index); and CDAI (Clinical Disease Activity Index). DAS28-ESR and CRP are measured taking into account the number of tender and swollen joints out of 28, ESR or CRP and patient's general health or global disease activity measured on a visual analogue scale of 100mm. CDAI was measured through tender and swollen 28-joint count, patient's global disease activity (from 0-10) and evaluator's global disease

activity (from 0-10). SDAI was measured by the arithmetic sum of tender and swollen 28-joint count, patient's and evaluator global assessment (both from 0-10) and CRP[16].

B) Morning-Evening Questionnaire Self-Assessment Version (MEQ-SA)- that is questionnaire to determine morningness-eveningness in human circadian rhythms. It has 19 multiple choice items with 4–5-point numerical scale. The sum gives a score ranging from 16 to 86; scores of 41 and below indicate "evening types", scores of 59 and above indicate "morning types", scores between 42-58 indicate "intermediate types" [17]. Data on MEQ-SA was collected simultaneously with data on disease activity.

As controls, patient's companions paired for sex and age were included.

Data was collected in frequency and contingency tables. Comparison of nominal data was done by chi-square and Fisher tests and of numerical data by the Mann Whitney and unpaired t test. Correlations studies of MEQ SA questionnaire and disease activities index were done by Spearman or Pearson test according to data distribution. The adopted significance was of 5%.

Results

The included sample had 156 individuals (77 RA patients and 79 controls). **Table 1** shows patient's demographic and pairing with controls data.

Table 1- Comparison of epidemiological data of rheumatoid arthritis (RA) patients and controls

	RA Patients n=77	Controls n=79	P
Female sex - n (%)	62 (80.5)	63 (79.7)	0.90
Median age – years- (IQR)	59.0 (52.5-62.0)	54.0 (50.0-63.0)	0.11
Current smokers – n (%)	11 (14.2)	7 (8.8)	0.28

In the RA sample the median disease duration was of 10.0 years (IQR=5.0-14.6) and 58.6% were positive for rheumatoid factor. The median SDAI was 3.19 (0.80-12.80); median CDAI was 4.00 (0-11.90); the median DAS28-ESR was 2.78 (2.15-3.61) and the median DAS28-CRP was 2.18 (1.60-3.33).

The comparative results of MEQ-SA between patients and controls are on **Figure 1**.

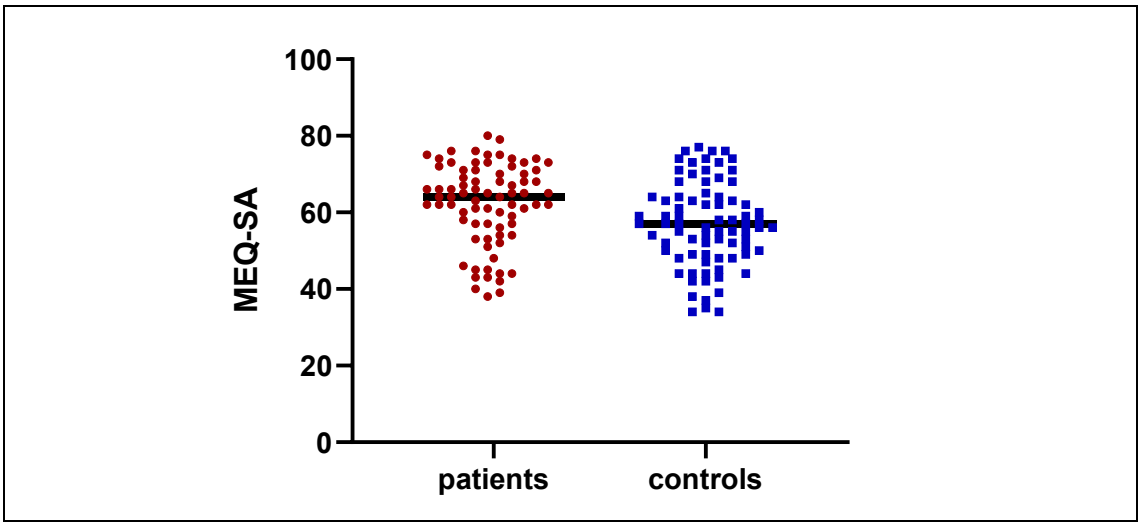

FIGURE 1 – Comparison of MEQ-SA results between rheumatoid arthritis (RA) patients and controls**.**

RA= median of 64.0 (56.5-71.0); controls= median of 57.0 (49.0-64.0); p=0.001
MEQ-SA= Morning-Afternoon Questionnaire Self-Assessment Version

In the RA sample, 55 (71.4%) were classified as morning types;19 (24.6%) as intermediate and 3 (3.8%) as evening types. In the control group 33 (41.7%) were classified as morning types; 40 (50.6%) in intermediated and 6 (7.5%) in the evening type; p=0.0009.

When the results of disease activity indexes were correlated with MEQ-SA the results on **table 2** were found. No correlations were observed.

Table 2- Correlation studies of Morning-Evening Questionnaire Self-Assessment Version with rheumatoid arthritis disease activity indexes.

	r	95% confidence interval	P
SDAI	-0.08	-0.31 to + 0.15	0.49
CDAI	-0.08	-0.31 to + 0.14	0.43
DAS28-ESR	-0.09	-0.32 to + 0.14	0.41
DAS28-CRP	-0.04	-0.27 to + 0.19	0.70

DAS28 =Disease activity score using 28 joints; CRP =C reactive protein, ESR =erythrocyte sedimentation rate, SDAI =Simplified Disease Activity Index, CDAI =Clinical Disease Activity Index.

No correlations were found of MEQ with age and disease duration, neither association with sex and presence of FR (all with p>0.05).

Discussion

The results of this study have shown that RA patients have morning chronotype more frequently than controls and that the indexes of MEQ-SA did not correlate with disease activity.

Finding an early chronotype in RA patients is in line with the observation that the circadian rhythm in individuals with this disease has also an early timing. This is considered to be due to altered temporal profile of melatonin with a more rapid increase at the start of the night yielding an earlier peak [13]. Melatonin is a hormone synthesized at the night primarily in the pineal gland and it is considered to have pro-inflammatory properties [7]. Cytokines and cortisol also have circadian fluctuations that are peculiar in RA individuals. Studies with sequential measurements of IL-6 show overnight variations of this cytokine with a peak in the early hours of the morning[18] . In RA the natural morning peak in cortisol level is blunted and the individual becomes unable to mount an appropriately enhanced response to combat inflammation [19]. Such variations could answer by the morning pain and stiffness seen on these patients. However, it was not possible to link the found early chronotype with disease activity indexes. The same was found by Habers et al. [19] that studied 121 RA patients. They also detected a preference for morning chronotypes in RA individuals without associations with inflammatory parameters. Although no explanation for this possible dissociation is found, it is important to note that it is unknown how chronotype and the internal circadian rhythm are related. Factors other than the circadian pacemaker may influence the chronotype such as physical activities, time and amount of exposure to light, social and work activities, genetic factors and even personality traits [20,21].

This study is limited by the small sample and the cross-sectional design. Studies with larger samples and with a prospective design that allow to observe possible changes in chronotype according to changes in disease activity are desired. The study of the rhythmicity of the inflammatory process in RA is important for the personalized chronotherapy by aligning the medication administration to chronotype for better efficacy.

Conclusion

RA patients had an earlier chronotype when compared to controls but without association with disease activity.

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